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Collagen Cross-Linking Using Riboflavin and Ultraviolet-A for Corneal Thinning Disorders: An Evidence-Based Analysis

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About the Medical Advisory Secretariat

Effective April 5, 2011, the Medical Advisory Secretariat (MAS) became a part of Health Quality Ontario (HQO), an independent body funded by the Ministry of Health and Long-Term Care. The mandate of the Medical Advisory Secretariat is to provide evidence-based recommendations on the coordinated uptake of health services and health technologies in Ontario to the Ministry of Health and Long-Term Care and to the health care system. This mandate helps to ensure that residents of Ontario have access to the best available and most appropriate health services and technologies to improve patient outcomes.

To fulfill its mandate, the Medical Advisory Secretariat conducts systematic reviews of evidence and consults with experts in the health care services community. The resulting evidence-based analyses are reviewed by the Ontario Health Technology Advisory Committee—to which MAS also provides a secretariat function—and published in the *Ontario Health Technology Assessment Series*.

About the Ontario Health Technology Assessment Series

To conduct its comprehensive analyses, the Medical Advisory Secretariat systematically reviews the available scientific literature, making every effort to consider all relevant national and international research; collaborates with partners across relevant government branches; consults with clinical and other external experts and developers of new health technologies; and solicits any necessary supplemental information.

In addition, the Secretariat collects and analyzes information about how a new technology fits within current practice and existing treatment alternatives. Details about the technology's diffusion into current health care practices add an important dimension to the review of the provision and delivery of the health technology in Ontario. Information concerning the health benefits; economic and human resources; and ethical, regulatory, social and legal issues relating to the technology assist decision-makers in making timely and relevant decisions to optimize patient outcomes.

The public consultation process is also available to individuals wishing to comment on an analysis prior to publication. For more information, please visit http://www.health.gov.on.ca/english/providers/program/ohtac/public_engage_overview.html.

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This evidence-based analysis was prepared by the Medical Advisory Secretariat for the Ontario Health Technology Advisory Committee and developed from analysis, interpretation, and comparison of scientific research and/or technology assessments conducted by other organizations. It also incorporates, when available, Ontario data and information provided by experts and applicants to the Medical Advisory Secretariat to inform the analysis. While every effort has been made to reflect all scientific research available, this document may not fully do so. Additionally, other relevant scientific findings may have been reported since completion of the review. This evidence-based analysis is current to the date of the literature review specified in the methods section. This analysis may be superseded by an updated publication on the same topic. Please check the Medical Advisory Secretariat website for a list of all evidence-based analyses: http://www.health.gov.on.ca/ohtas.

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Abbreviations

BCVA	Best corrected visual acuity
BSCVA	Best spectacle-corrected visual acuity
CCT	Central Corneal Thinning
CLEK	Collaborative Longitudinal Evaluation of Keratoconus
CXL	Corneal collagen cross-linking
ICRS	Intrastromal corneal ring segment
IOL	Intraocular lens
IOP	Intraocular pressure
KC	Keratoconus
LASIK	Laser in situ keratomileusis
LogMAR	Logarithm of the minimum angle of resolution
NR	Not reported
PKP	Penetrating keratoplasty
PMCD	Pellucid marginal corneal degeneration
PRK	Photorefractive keratectomy
RCT	Randomized controlled trial
SE	Spherical equivalent
UCVA	Uncorrected visual acuity
UVA	Ultraviolet-A
VA	Visual acuity

Executive Summary

Objective

The main objectives for this evidence-based analysis were to determine the safety and effectiveness of photochemical corneal collagen cross-linking with riboflavin (vitamin B_2) and ultraviolet-A radiation, referred to as CXL, for the management of corneal thinning disease conditions. The comparative safety and effectiveness of corneal cross-linking with other minimally invasive treatments such as intrastromal corneal rings was also reviewed. The Medical Advisory Secretariat (MAS) evidence-based analysis was performed to support public financing decisions.

Subject of the Evidence-Based Analysis

The primary treatment objective for corneal cross-linking is to increase the strength of the corneal stroma, thereby stabilizing the underlying disease process. At the present time, it is the only procedure that treats the underlying disease condition. The proposed advantages for corneal cross-linking are that the procedure is minimally invasive, safe and effective, and it can potentially delay or defer the need for a corneal transplant. In addition, corneal cross-linking does not adversely affect subsequent surgical approaches, if they are necessary, or interfere with corneal transplants. The evidence for these claims for corneal cross-linking in the management of corneal thinning disorders such as keratoconus will be the focus of this review.

The specific research questions for the evidence review were as follows:

1. Technical: How technically demanding is corneal cross-linking and what are the operative risks?
2. Safety: What is known about the broader safety profile of corneal cross-linking?
3. Effectiveness - Corneal Surface Topographic Affects:
    a. What are the corneal surface remodeling effects of corneal cross-linking?
    b. Do these changes interfere with subsequent interventions, particularly corneal transplant known as penetrating keratoplasty (PKP)?
4. Effectiveness -Visual Acuity:
    a. What impacts does the remodeling have on visual acuity?
    b. Are these impacts predictable, stable, adjustable and durable?
5. Effectiveness - Refractive Outcomes: What impact does remodeling have on refractive outcomes?
6. Effectiveness - Visual Quality (Symptoms): What impact does corneal cross-linking have on vision quality such as contrast vision, and decreased visual symptoms (halos, fluctuating vision)?
7. Effectiveness - Contact lens tolerance: To what extent does contact lens intolerance improve after corneal cross-linking?
8. Vision-Related QOL: What is the impact of corneal cross-linking on functional visual rehabilitation and quality of life?
9. Patient satisfaction: Are patients satisfied with their vision following the procedure?
10. Disease Process:
    a. What impact does corneal cross-linking have on the underling corneal thinning disease process?
11. Does corneal cross-linking delay or defer the need for a corneal transplant?
12. What is the comparative safety and effectiveness of corneal cross-linking compared with other minimally invasive treatments for corneal ectasia such as intrastromal corneal rings?

Clinical Need: Target Population and Condition

Corneal ectasia (thinning) disorders represent a range of disorders involving either primary disease conditions, such as keratoconus (KC) and pellucid marginal corneal degeneration, or secondary iatrogenic conditions, such as corneal thinning occurring after laser in situ keratomileusis (LASIK) refractive surgery.

Corneal thinning is a disease that occurs when the normally round dome-shaped cornea progressively thins causing a cone-like bulge or forward protrusion in response to the normal pressure of the eye. The thinning occurs primarily in the stroma layers and is believed to be a breakdown in the collagen process. This bulging can lead to irregular astigmatism or shape of the cornea. Because the anterior part of the cornea is responsible for most of the focusing of the light on the retina, this can then result in loss of visual acuity. The reduced visual acuity can make even simple daily tasks, such as driving, watching television or reading, difficult to perform.

Keratoconus is the most common form of corneal thinning disorder and involves a noninflammatory chronic disease process of progressive corneal thinning. Although the specific cause for the biomechanical alterations in the corneal stroma is unknown, there is a growing body of evidence suggesting that genetic factors may play an important role. Keratoconus is a rare disease (< 0.05% of the population) and is unique among chronic eye diseases because it has an early onset, with a median age of 25 years. Disease management for this condition follows a step-wise approach depending on disease severity. Contact lenses are the primary treatment of choice when there is irregular astigmatism associated with the disease. Patients are referred for corneal transplants as a last option when they can no longer tolerate contact lenses or when lenses no longer provide adequate vision.

Keratoconus is one of the leading indications for corneal transplants and has been so for the last 3 decades. Despite the high success rate of corneal transplants (up to 20 years) there are reasons to defer it as long as possible. Patients with keratoconus are generally young and a longer-term graft survival of at least 30 or 40 years may be necessary. The surgery itself involves lengthy time off work and postsurgery, while potential complications include long-term steroid use, secondary cataracts, and glaucoma. After a corneal transplant, keratoconus may recur resulting in a need for subsequent interventions. Residual refractive errors and astigmatism can remain challenges after transplantation, and high refractive surgery and regraft rates in KC patients have been reported. Visual rehabilitation or recovery of visual acuity after transplant may be slow and/or unsatisfactory to patients.

Description of Technology/Therapy

Corneal cross-linking involves the use of riboflavin (vitamin B_2) and ultraviolet-A (UVA) radiation. A UVA irradiation device known as the CXL® device (license number 77989) by ACCUTECH Medical Technologies Inc. has been licensed by Health Canada as a Class II device since September 19, 2008. An illumination device that emits homogeneous UVA, in combination with any generic form of riboflavin, is licensed by Health Canada for the indication to slow or stop the progression of corneal thinning caused by progressive keratectasia, iatrogenic keratectasia after laser-assisted in situ keratomileusis (LASIK) and pellucid marginal degeneration. The same device is named the UV-X® device by IROCMedical, with approvals in Argentina, the European Union and Australia.

UVA devices all use light emitting diodes to generate UVA at a wavelength of 360-380 microns but vary in the number of diodes (5 to 25), focusing systems, working distance, beam diameter, beam uniformity and extent to which the operator can vary the parameters. In Ontario, CXL is currently offered at over 15 private eye clinics by refractive surgeons and ophthalmologists.

The treatment is an outpatient procedure generally performed with topical anesthesia. The treatment consists of several well defined procedures. The epithelial cell layer is first removed, often using a blunt spatula in a 9.0 mm diameter under sterile conditions. This step is followed by the application of topical 0.1% riboflavin (vitamin B_2) solution every 3 to 5 minutes for 25 minutes to ensure that the corneal stroma is fully penetrated. A solid-state UVA light source with a wavelength of 370 nm (maximum absorption of riboflavin) and an irradiance of 3 mW/cm^2 is used to irradiate the central cornea. Following treatment, a soft bandage lens is applied and prescriptions are given for oral pain medications, preservative-free tears, anti-inflammatory drops (preferably not nonsteroidal anti-inflammatory drugs, or NSAIDs) and antibiotic eye drops. Patients are recalled 1 week following the procedure to evaluate re-epithelialization and they are followed-up subsequently.

Evidence-Based Analysis Methods

A literature search was conducted on photochemical corneal collagen cross-linking with riboflavin (vitamin B_2) and ultraviolet-A for the management of corneal thinning disorders using a search strategy with appropriate keywords and subject headings for CXL for literature published up until April 17, 2011. The literature search for this Health Technology Assessment (HTA) review was performed using the Cochrane Library, the Emergency Care Research Institute (ECRI) and the Centre for Reviews and Dissemination. The websites of several other health technology agencies were also reviewed, including the Canadian Agency for Drugs and Technologies in Health (CADTH) and the United Kingdom's National Institute for Clinical Excellence (NICE). The databases searched included OVID MEDLINE, MEDLINE IN-Process and other Non-Indexed Citations such as EMBASE.

As the evidence review included an intervention for a rare condition, case series and case reports, particularly for complications and adverse events, were reviewed. A total of 316 citations were identified and all abstracts were reviewed by a single reviewer for eligibility. For those studies meeting the eligibility criteria, full-text articles were obtained. Reference lists were also examined for any additional relevant studies not identified through the search.

Inclusion Criteria

- English-language reports and human studies
- patients with any corneal thinning disorder
- reports with CXL procedures used alone or in conjunction with other interventions
- original reports with defined study methodology
- reports including standardized measurements on outcome events such as technical success, safety effectiveness, durability, vision quality of life or patient satisfaction
- systematic reviews, meta-analyses, randomized controlled trials, observational studies, retrospective analyses, case series, or case reports for complications and adverse events

Exclusion Criteria

- nonsystematic reviews, letters, comments and editorials
- reports not involving outcome events such as safety, effectiveness, durability, vision quality or patient satisfaction following an intervention with corneal implants
- reports not involving corneal thinning disorders and an intervention involving CXL

Summary of Evidence Findings

In the Medical Advisory Secretariat evidence review on corneal cross-linking, 65 reports (16 case reports) involving 1403 patients were identified on the use of CXL for managing corneal thinning disorders. The

reports were summarized according to their primary clinical indication, whether or not secondary interventions were used in conjunction with CXL (referred to as CXL-Plus) and whether or not it was a safety-related report.

The safety review was based on information from the cohort studies evaluating effectiveness, clinical studies evaluating safety, treatment response or recovery, and published case reports of complications. Complications, such as infection and noninfectious keratitis (inflammatory response), reported in case reports, generally occurred in the first week and were successfully treated with topical antibiotics and steroids. Other complications, such as the cytotoxic effects on the targeted corneal stroma, occurred as side effects of the photo-oxidative process generated by riboflavin and ultraviolet-A and were usually reversible.

The reports on treatment effectiveness involved 15 pre-post longitudinal cohort follow-up studies ranging from follow-up of patients' treated eye only, follow-up in both the treated and untreated fellow-eye; and follow-up in the treated eye only and a control group not receiving treatment. One study was a 3-arm randomized control study (RCT) involving 2 comparators: one comparator was a sham treatment in which one eye was treated with riboflavin only; and the other comparator was the untreated fellow-eye. The outcomes reported across the studies involved statistically significant and clinically relevant improvements in corneal topography and refraction after CXL. In addition, improvements in treated eyes were accompanied by worsening outcomes in the untreated fellow-eyes. Improvements in corneal topography reported at 6 months were maintained at 1- and 2-year follow-up. Visual acuity, although not always improved, was infrequently reported as vision loss. Additional procedures such as the use of intrastromal corneal ring segments, intraocular lenses and refractive surgical practices were reported to result in additional improvements in topography and visual acuity after CXL.

Considerations for Ontario Health System

The total costs of providing CXL therapy to keratoconus patients in Ontario was calculated based on estimated physician, clinic, and medication costs. The total cost per patient was approximately $1,036 for the treatment of one eye, and $1,751 for the treatment of both eyes. The prevalence of keratoconus was estimated at 4,047 patients in FY2011, with an anticipated annual incidence (new cases) of about 148 cases. After distributing the costs of CXL therapy for the FY2011 prevalent keratoconus population over the next 3 years, the estimated average annual cost was approximately $2.1 million, of which about $1.3 million would be physician costs specifically.

Conclusion

Corneal cross-linking effectively stabilizes the underlying disease, and in some cases reverses disease progression as measured by key corneal topographic measures. The affects of CXL on visual acuity are less predictable and the use of adjunct interventions with CXL, such as intrastromal corneal ring segments, refractive surgery, and intraocular lens implants are increasingly employed to both stabilize disease and restore visual acuity. Although the use of adjunct interventions have been shown to result in additional clinical benefit, the order, timing, and risks of performing adjunctive interventions have not been well established.

Although there is potential for serious adverse events with corneal UVA irradiation and photochemical reactions, there have been few reported complications. Those that have occurred tended to be related to side effects of the induced photochemical reactions and were generally reversible. However, to ensure

that there are minimal complications with the use of CXL and irradiation, strict adherence to defined CXL procedural protocols is essential.

Keywords

Keratoconus, corneal cross-linking, corneal topography, corneal transplant, visual acuity, refractive error.

Background

Objective of Analysis

The overall scope of the project was to determine the role of photochemical corneal collagen cross-linking with riboflavin (vitamin B_2) and ultraviolet-A radiation, referred to as CXL, for the management of corneal thinning disease conditions. The main objectives for the evidence review were to determine the safety and effectiveness of CXL for the management of corneal thinning disorders. The comparative safety and effectiveness of CXL with other minimally invasive treatments such as intrastromal corneal rings was also reviewed.

Clinical Need

Corneal ectasia (thinning) disorders represent a range of disorders and can involve either primary disease conditions such as keratoconus (KC) and pellucid marginal corneal degeneration (PMCD) or secondary iatrogenic conditions such as corneal ectasia occurring after laser in-situ keratomileusis (LASIK) refractive surgery. Corneal thinning is a disease that occurs when the normally round dome-shaped cornea (the clear outer area of the eye) progressively thins, causing a cone-like bulge or forward protrusion in response to the normal pressure of the eye pushing out on the thinned areas of the cornea. (1) The thinning occurs primarily in the stroma layers and is believed to be a breakdown in the collagen process.

This bulging can lead to an irregularly shaped cornea and because the anterior part of the cornea is responsible for most of the focusing of the light on the retina, can results in loss of visual acuity, both uncorrected visual acuity (UCVA) and best-spectacle corrected visual acuity (BSCVA). The visual acuity loss is secondary to high irregular astigmatism that can occur with and without myopia. (2) The reduced visual acuity can make even simple daily tasks, such as driving, watching television or reading, difficult to perform. The subsequent corneal protrusion or distortions can also result in corneal scarring and treatment-related sequelae such as abrasions from contact lenses.

There are a variety of corneal thinning disorders but it is unknown if these represent distinct forms of the disease or variants of the same disease process. Keratoconus is the most common form of thinning disorders and involves a noninflammatory chronic disease process of progressive corneal thinning. (3) Although the condition may initially present in one eye, it is a progressive disorder and eventually affects both eyes. (4) In keratoconus, localized thinning can occur in a variety of patterns, but when it occurs in the inferior cornea in a crescent-type pattern it is referred to as pellucid marginal corneal degeneration (PMCD). (5)

Etiology

Keratoconus leads to biomechanical alterations of the cornea involving the collagen scaffold and collagen compound, and to their bonding with the collagen fibrils. (6;7) The biochemical resistance of the cornea of KC patients is half that of the normal value. (8) The specific cause for these biochemical alterations, however, is unknown. There is a growing body of evidence suggesting that genetic factors may play an important role. (4) The proportion of persons with KC reported to have a positive family history of the disease ranged from 6% to 15%. The National Eye Institute (NEI) in the United States sponsored a multicenter longitudinal follow-up cohort study, the Collaborative Longitudinal Evaluation of Keratoconus (CLEK), which found that out of 1,209 keratoconus patients recruited over a 1-year period (May 1995 to June 1996), 13.5% reported a family history of KC. (2) Also reported has been an occurrence of the disease in second- and third-generation studies and a high concordance in monozygotic

twins**.** (9;10) A study evaluating corneal topography in first-degree relatives of patients with KC found an 11% (8/72) incidence of the disease, compared to 0.05% in the general population. (11)

Additional information about KC patients is available from the CLEK study, the largest cohort study of keratoconus patients to date. (2) A reported high percentage of atopia (53%) has unknown clinical significance for these patients. Unlike findings in smaller clinical series, no patients reported systemic diseases such as Down's syndrome, Marfan syndrome, focal dermal hypoplasia, Ehlers-Danlos syndrome, oculodentodigital syndrome, osteogenesis imperfecta, or Reigers anomaly.

Diagnosis

Diagnosis of KC depends on the methods used and can be difficult for several reasons. The onset of the disease itself is gradual and in some patients may never progress beyond subtle irregular astigmatism for which patients may not seek medical or optometric care. Subclinical forms (forme fruste) of keratoconus are particularly difficult to diagnose. Representative diagnostic patterns for subclinical forms have been described by some as having a corneal topographic pattern of at least one of the following: Inferior-Superior (I-S) asymmetry index> 1.4 diopters (D), central corneal power > 47.2 D, or a fellow-eye diagnosed with keratoconus. (12)

Computer-assisted videophotokeratoscopes provides a means to detect subtle changes and quantitative measures of corneal surface topographic changes. (13) The most commonly employed grading or classification system for KC is Amsler-Krumeich scale. (3;14) This classification system comprises 4 stages of disease based on the degree of corneal topography, myopia or induced astigmatism, clinical signs (Vogl's striae, etc), central corneal scarring, and corneal thickness. The disease stages are as follows:

- Stage 1 - eccentric corneal steepening, induced myopia and/or astigmatism <5 D, corneal radii ≤ 48 D, slit lamp findings (Vogl's striae), no scars
- Stage 2 - induced myopia and/or astigmatism >5 D <8 D, corneal radii ≤ 53 D, no central scars, corneal thickness ~400 µm
- Stage 3 - induced myopia and/or astigmatism >8 D <10 D, corneal radii >53 D, no central scars, corneal thickness 200 to 400 µm
- Stage 4 - refraction not measurable, corneal radii >55D, central scars, perforation, corneal thickness 200 µm.

Disease prevalence and natural history

Keratoconus is a rare disorder with estimates of prevalence ranging from a rate of approximately 50 to 230 per 100,000 population. (15) An American population-based 48-year survey estimated an overall prevalence of 54.5 per 100,000, with an overall annual incidence rate of 2.0 per 100,000. (16) The age-adjusted prevalence rate was significantly ($P < .05$) higher in males than in females (69.5 vs. 39.2 per 100,000).

Keratoconus is unique in chronic eye diseases because it has an early onset. (17) In the Kennedy et al. study of 64 cases, the median age at disease onset was reported to be 25 years (ranging from 12 to 77 years) and the diagnosis was unilateral in 41% at diagnosis. In the CLEK study, the median age at study entry was 39.3 years and the impact of KC on vision was already detectable. (2) The variable visual acuity of KC patients in this study (Table 1) shows that 22% already had fair or worse (≥ 20/40) best-corrected visual acuity (BCVA) in their worst eye. A Snellen visual acuity range of up to 20/40 is interpreted as a range in which many individuals can function without optical correction. (18) A visual

acuity above 20/40 is the most common cut-off level for unrestricted drivers' licences, and 20/200 or worse is part of the legal definition of blindness.

Table 1: Baseline Visual Acuity of Keratoconus Patients in the CLEK Cohort Study*

Vision Quality	Best Corrected Visual Acuity Range	Snellen Visual Acuity Better Eye, No. (%)	Snellen Visual Acuity Worse Eye, No. (%)
Normal range	20/20 or better	538 (44.7)	169 (14.0)
Normal (without optical correction)	20/21 to 20/40	612 (50.8)	769 (63.9)
Fair	20/40 to 20/69	43 (3.6)	183 (15.2)
Poor	20/70 to 20/199	10 (0.8)	71 (5.9)
Poor (legal definition blindness)	20/200 or worse	1 (0.08)	12 (0.9)

*CLEK indicates Collaborative Longitudinal Evaluation of Keratoconus

Disease Management

Disease management for corneal thinning disorders such as KC generally follows a basic treatment algorithm in a step-wise approach, depending on disease severity. (19) In the early stages of the disease, initial visual disturbances in keratoconus may be managed with spectacles. Rigid gas-permeable contact lenses are the primary treatment of choice when there is irregular astigmatism associated with the disease. Sometimes hydrogel lenses are used in later stages with rigid lenses in a piggyback fashion (hard lens placed on top of soft lens) to correct vision. Contact lenses may fail because patients become intolerant and unable to wear them, or they do not provide sufficient visual acuity to meet the patient's needs. As shown in Table 2, the baseline visual correction reported for the CLEK cohort of KC patients displays the variability and custom fitting in refractive correction for these patients. (2) Only 3.5% of the patients were unaided in both eyes. The type of contact lenses used ranged from rigid gas-permeable (65%) to soft lenses, piggyback contact lens and hybrid (soft and hard) lenses.

Table 2: Baseline Visual Correction in Patients in CLEK Cohort Study*

Type of Correction	Number of Patients, (%)
Same in Both Eyes	
Unaided	43 (3.6)
Glasses	194 (16.1)
Contact lenses	321 (26.6)
Glasses and contacts	571 (47.2)
Different in Each Eye	
One eye unaided and fellow-eye contact lenses	37 (3.1)
One eye glasses and contacts with fellow-eye unaided	2 (0.2)
One eye glasses and contacts with fellow-eye contact lenses	1 (0.1)
One eye glasses and contacts with fellow-eye glasses	40 (3.6)

*CLEK indicates Collaborative Longitudinal Evaluation of Keratoconus

Vision Quality of Life

The impact of declining visual acuity and an uncertain variable disease progression has profound affects for KC patients, who are often diagnosed in adolescence or early adulthood. The National Eye Institute-Visual Function Questionnaire (NEI-VFQ) is a vision-related quality of life instrument designed to measure a patient's perception of visual function and quality of life. (17) The reported VFQ scores for each of the 12 subscales were significantly ($P < .05$) poorer for patients with KC than for non-KC patients of similar age wearing rigid gas permeable contact lenses. The reported VFQ subscores for KC patients were rated at levels between those reported by patients with extensive macular degeneration and by those with advanced macular degeneration, except for colour vision and general health. The ocular pain score for KC patients, however, was significantly worse than it was even for patients with advanced macular degeneration.

Developing utility values is one method of assessing the value of vision or the impact of declining vision on individuals. In this case, the time trade-off technique was used to measure how valuable a level of visual acuity is to an individual as measured by the hypothetical trade-off between living fewer years but with better vision. A significant relationship (Table 3) between decreasing visual acuity in the better-seeing eye and ocular utility values was evident in a study of 500 patients with ocular disorders. (20) The utility values for vision were more pronounced when comparing utility values across disease states (Table 4). (20) The utility at the first level of vision loss (around 20/40) is rated similarly to a myocardial infarction, while visual acuity around 20/200 (or at a definition of legal blindness) corresponds to a moderate stroke, after which persons require some help but are still ambulatory.

Table 3: Patient-based Time Tradeoff Utility Values Associated with Visual Acuity Levels in the Better Seeing Eye

Patients With Ocular Disorders, N	Vision Range In Better Seeing Eye	Mean Utility Value	Standard Deviation	95% Confidence Interval
127	20/20 to 20/25	0.88	0.15	0.85–0.91
218	20/30 to 20/50	0.81	0.21	0.78–0.84
83	20/60 to 20/100	0.72	0.21	0.67–0.77
72	20/200 to no light perception	0.61	0.19	0.57–0.65

Table 4: Patient-based Time Tradeoff Utility Values Across Disease States

Disease State/Event	Time Tradeoff Utility Value
Diabetes	0.88
Visual acuity 20/40 (most common cut off for driver's licence)	0.80
Myocardial infarction, moderate	0.80
Stroke, moderate (requiring some help but able to walk)	0.69
Visual acuity 20/200 (definition of legal blindness)	0.66
Osteoarthritis hip, mild	0.69
Ulcerative colitis, Preoperative	0.58
Renal disease, end-stage, home dialysis	0.49
Total blindness (no light perception)	0.26
Stroke, severe (total paralysis)	0.30

Surgical Interventions

Prior to penetrating keratoplasty (corneal transplantation), a range of surgical options will be considered in order to delay or avoid transplantation. (1;3) These options have been generally classified as subtractive or additive procedures. Subtractive procedures—in which corneal tissue is removed to alter corneal surfaces—are not reversible. These procedures involve various techniques, such as radical keratotomy, asymmetric kerotomy, photorefractive keratectomy (PRK), photo astigmatic refractive keratectomy, phototherapeutic keratotomy, and LASIK. Because they result in further tissue loss, these procedures are not an optimal approach to a disease that already involves progressive tissue loss.

There are fewer additive procedures to reinforce corneal tissue, but intrastromal corneal rings (ICRS) (21) and, more recently, CXL (6;7), are 2 techniques that do reinforce the cornea. However CXL, unlike ICRS, is intended to stabilize the underlying disease process by strengthening the corneal stromal collagen.

Corneal Transplant

Patients are referred for corneal transplant as a last option when they can no longer tolerate contact lenses, or when lenses no longer provide adequate vision correction. Corneal transplant becomes necessary when severe irregular corneal astigmatism or stromal opacities develop. In a longitudinal cohort study of KC patients, decreasing visual function in almost 20 years of follow-up led to corneal transplant in 18.8% (12 of 64) of patients. (16) The interval from diagnosis to corneal transplant ranged from less than 2 years to 46 years. The interval from diagnosis to transplant in the fellow-eye of KC patients, however, was much shorter, particularly so in patients with high measures of corneal surface abnormalities (5.48 vs. 22.11 years $P = 0.018$). (4)

Keratoconus has been one of the leading indications for corneal transplants (11% to 16%) for the last 3 decades. (22;23) The overall corneal graft survival rate reported for 3992 cases referred to a tertiary care center was 82% at 10-year follow-up; the regraft survival rate, however, was only 41%. (24) Grafts for KC had higher survival rates—92% at the 10-year mark. A follow-up study of 112 KC eyes of 84 patients (mean 13.8 years, range 0.5 to 30.4 years) treated by 18 surgeons between 1970 and 1983 resulted in a graft failure in 7 of 112 transplanted eyes. (25) Graft survival estimates at 20 and 25 years were 93.7% (95% CI; 88.1–99.3) and 85.4% (95% CI; 72.8–98), respectively.

Despite the success of corneal transplants, there are reasons to defer the transplant procedure for as long as possible. The surgery itself necessitates lengthy time off work as postoperative recovery ranges from 4 to 12 weeks (mean 6.7 ± 3.1 wks). Following surgery, there are also potential complications stemming from long-term steroid use, secondary cataracts, glaucoma, etc. After the transplant, recurrent KC is possible, necessitating subsequent interventions. The refractive surgery rate for high astigmatism and the regraft rate in KC patients have been reported to be 26.8% and 9%, respectively. (23;26) In another report, (25) recurrent KC was diagnosed by breaks in Bowman's layer (a thin layer of cornea between the outer layer of stratified epithelium and the substantia propria) in 6 eyes (5.4%) of 5 (6.%) patients and high irregular astigmatism was suggestive of KC in an additional 8 eyes (7.1%).

Residual regular and irregular astigmatism, myopia and hyperopia can remain challenging after transplantation. Visual rehabilitation or recovery of visual acuity may be slow and/or unsatisfactory to patients. Limitations in satisfaction with vision and contact lens tolerance following transplant have been reported. (27) Only 62% felt that the post-transplantation result was as expected or better postoperatively. However, 9.5% of subjects wore no vision correction of any type. Tolerance for contact lenses improved in many (67% easier to wear); although 25% reported no difference and 8% reported that contact lenses were more difficult to wear.

Corneal Collagen Cross-Linking

Regulatory Status

Corneal cross-linking involves the use of riboflavin (vitamin B_2) and ultraviolet-A (UVA) radiation. An UVA irradiation device known as the CXL® device (license number 77989) by ACCUTECH Medical Technologies Inc. has been licensed by Health Canada as a Class II device since September 19, 2008. An illumination device that emits homogeneous UVA, in combination with any generic form of riboflavin (vitamin B_2), it is licensed by Health Canada for the indication to slow or stop the progression of corneal thinning caused by progressive keratectasia, iatrogenic keratectasia after LASIK and pellucid marginal degeneration. The same device is called the UV-X® device by IROCMedical with approvals in Argentina, the European Union, and Australia.

UVA devices all use light-emitting diodes to generate UVA at a wavelength of 360-380 microns, but the devices vary in terms of the number of diodes (5 to 25) they have, their focusing systems, working distance, beam diameter, beam uniformity, and the extent to which the operator can vary the parameters. In Ontario, CXL is currently offered by refractive surgeons and ophthalmologists at more than 15 private eye clinics.

Treatment Procedures

Corneal cross-linking is an outpatient procedure generally performed with topical anesthesia. The treatment consists of several well-defined procedures. (28) The epithelial cell layer is first removed, often using a blunt spatula, in a 9.0 mm diameter under sterile conditions. Next, a topical 0.1% riboflavin (vitamin B_2) solution is applied every 3-5 minutes for 25 minutes to ensure that the corneal stroma is fully penetrated. A solid-state UVA light source with a wavelength of 370 nm (maximum absorption of riboflavin) and an irradiance of 3 mW/cm^2 is used to irradiate the central cornea. Following treatment, a soft bandage lens is applied and prescriptions given for oral pain medications, preservative-free tears, anti-inflammatory drops and antibiotic eye drops. Patients are recalled at 1-week postprocedure to evaluate re-epithelialization, with subsequent follow-up appointments to monitor status.

Mechanism of Action

Riboflavin acts as a photosensitizer and has an absorption peak for UVA wavelength of approximately 370 microns. (28) Riboflavin-saturated cornea exposed to UV irradiation at this wavelength fluoresces and is excited into a triplet state with subsequent generation of singlet oxygen (mainly) and superoxide anion radicals. The reactive oxygen species leads to the formation of covalent bonds bridging amino acids of collagen fibrils by oxidative process dependent on the presence of O^2 and enhanced by deuterium oxide. The increased bonding in the corneal stromal layer leads to an increased "stiffness" of the cornea.

Potential Risks and Limitations

There are potential safety concerns related to CXL. Different types of risks relate to the different stages of the procedure, including the initial creation of an epithelial defect, the direct and indirect effects of the UVA irradiation of the central cornea, and the subsequent photochemical process occurring with riboflavin and UVA.

The creation of an epithelial defect—by removing the defensive layer of the cornea—potentially increases the risk of opportunistic infections. Re-epithelialization after the procedure may be delayed or abnormal, resulting in complications. The target area for irradiation is the underlying stroma or middle layer of the cornea. In order to ensure that deeper ocular structures such as the endothelium, lens, or retina are not

affected by irradiation, only patients with central corneal depth of at least 400 µm are eligible for the treatment. The width of the treatment zone is also important to decreasing the risk of irradiation to the limbus and to protecting the limbal stem cells from any cytotoxic effects of the photo-oxidative process. The delivery of UVA must also involve a uniform UVA source in order to avoid hot spots that could damage the cornea.

Technical results can be unsatisfactory for several reasons. It is not known how much actual corneal stiffening is required from the CXL process in individual cases and it is not possible to moderate or tailor the procedure. In some cases, there may be an induced state of under- or over-corneal stiffening, leading to corrections which may have undesired effects on the corneal surface. Treatment with CXL is not always an option for patients with corneal thinning. In addition, those with central corneal scarring would not benefit from CXL and as detailed earlier, those without an adequate corneal thickness would be at increased risk for irradiation damage to deeper ocular critical structures. Finally, patients who are primarily interested in having their vision improved would also not be candidates for CXL as the procedure is not indicated for this outcome, although some patients may experience improved vision following the CXL.

Clinical Indications

CXL has primarily been introduced and evaluated as a treatment for corneal thinning disorders, such as keratoconus, that are in a progressive state. Although CXL has been investigated for utility in other disease states such as infectious keratitis (29-31) and bullous keratopathy (32;33), the reports have involved a few small case series and results have been inconsistent. The studies are summarized below in Table 5.

Table 5: Reports of Other Indications for Corneal Collagen Cross-Linking*

Author, Year	Site Country	Study Design	Study Population	Study Follow-up
Ghanem R, 2010 (32)	Department of Ophthalmology University of San Paulo and Sadalla Amin Ghanem Eye Hospital, Santa Catarina, Brazil	Case series	14 p (6 M, 8F) - 14 e Mean age 71.14 yrs± 11.7 (range 53 to 89 yrs) Bullous keratopathy	6 months
Iseli H, 2008 (29)	Institute for Refractive and Ophthalmic Surgery, Zurich, Switzerland	Case series	5 p (2 M, 3 F) Age range 27-66 years Therapy resistant infectious keratitis associated corneal melting, 4 with prior LASIK	Range 1-9 months
Makdoumi K, 2010 (30)	Department Ophthalmology, Orebro University Hospital, Orebro, Sweden	Case series	6 p - 7 e Severe infectious keratitis and corneal melting in all cases	Range 1-6 months

Author, Year	Site Country	Study Design	Study Population	Study Follow-up
Mazzotta C, 2011 (34)	Department Ophthalmology, Siena University, Italy	Case report	38-year-old male Visual fluctuations and declining visual acuity, after radical keratotomy for KC-related myopia	12-months
Moren H, 2010 (31)	Department Ophthalmology, Regional Hospital Vasteras, Sweden	Case report	25-year old female Severe keratitis	9 months
Wollensak G, 2009 (33)	Eye Laser Institute, Department of Ophthalmology, Martin Luther University, Germany	Case reports	3 cases (3 e) Bullous keratopathy due to 3 different conditions-pseudophakia, corneal transplant rejection and Fuch's endothelial dystrophy	8 months

*e indicates eyes; M, male; F, female

Evidence-Based Analysis

Research Question(s)

The main objectives for this evidence review were to determine the safety and effectiveness of CXL for the management of corneal thinning disorders. The primary treatment objective for CXL is to stabilize the underlying disease process by strengthening the stromal collagen network in order to delay or defer the need for corneal transplant. The advantage of CXL is that it is a minimally invasive treatment that can be performed on an outpatient basis.

The analyses in this evidence review centered on the following research questions*:*

1. Technical:
    a. How technically demanding is corneal cross-linking and what are the operative risks?
2. Safety:
    a. What is known about the broader safety profile of corneal cross-linking?
    b. What is the comparative safety and effectiveness of corneal cross-linking compared with other minimally invasive treatments for corneal ectasia such as intrastromal corneal rings?
3. Effectiveness—Corneal Surface Topographic effects:
    a. What corneal surface remodeling effects does corneal cross-linking have?
    b. Do these changes interfere with subsequent interventions, particularly corneal transplant known as penetrating keratoplasty (PKP)?
4. Effectiveness—Visual Acuity:
    a. What effects does remodeling have on visual acuity?
    b. Are these effects predictable, stable, adjustable, and durable?
5. Effectiveness—Refractive Outcomes:
    a. What impact does remodeling have on refractive outcomes?
6. Effectiveness—Visual Quality (Symptoms):
    a. What impact does corneal cross-linking have on vision quality such as contrast vision, and decreased visual symptoms (halos, fluctuating vision)?
7. Effectiveness—Contact lens tolerance:
    a. To what extent was contact lens intolerance improved after corneal cross-linking?
8. Vision-related quality of life (QOL):
    a. What is the impact of corneal cross-linking on functional visual rehabilitation and quality of life?
9. Patient satisfaction:
    a. Are patients satisfied with their vision following the procedure?
10. Disease Process:
    a. What impact does corneal cross-linking have on the underlying corneal thinning disease process?
    b. Does corneal cross-linking delay or defer the need for a corneal transplant?

Methods

Search Strategy

A literature search was conducted on corneal collagen cross-linking with riboflavin (vitamin B_2) and ultraviolet-A radiation for corneal thinning disorders. The search strategies, using appropriate keywords and subject headings for CXL, are outlined in Appendix1A. The literature search was performed using the Cochrane Library, the Emergency Care Research Institute (ECRI) and the Centre for Reviews and Dissemination. The websites of several other health technology agencies were also reviewed, including those of the Canadian Agency for Drugs and Technologies in Health (CADTH) and the United Kingdom's National Institute for Clinical Excellence (NICE).

Databases Searched

The databases searched for literature published until April 17, 2011 included OVID MEDLINE, MEDLINE IN-Process and other Non-Indexed Citations such as EMBASE, the Cochrane Library and the Centre for Reviews and Dissemination. As the evidence review included an intervention for a rare condition (keratoconus), case series and case reports with particular regard to complications and adverse events were reviewed.

Inclusion Criteria

- English-language reports and human studies
- patients with any corneal thinning disorder
- reports with CXL procedures used alone or in conjunction with other interventions
- original reports with defined study methodology
- reports including standardized measurements on outcome events such as technical success, safety, effectiveness, durability, vision quality of life or patient satisfaction
- systematic reviews, meta-analyses, randomized controlled trials, observational studies, retrospective analyses, case series, or case reports for complications and adverse events

Exclusion Criteria

- nonsystematic reviews, letters, comments and editorials
- reports not involving outcome events such as safety, effectiveness, durability, vision quality or patient satisfaction following an intervention with CXL
- reports not involving corneal thinning disorders and a CXL intervention

The citations from different sources were merged into one database using Reference Manager software. In total**,** 316 citations were identified. The citation lists were reviewed, and articles were excluded based on title and abstract. All abstracts were then reviewed for eligibility by a single reviewer and full-text articles were obtained for studies meeting the eligibility criteria. Reference lists were also examined for any additional relevant studies not identified through the search.

Additional Information Sources

Consultations were held with clinical experts and industry representatives.

Assessment of Quality of Evidence

The quality of evidence was assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology (35) as high, moderate, low or very low. The potential effects of further evidence on decision-making were also rated according to the following GRADE definitions:

High	Further research is very unlikely to change our confidence in the estimate of effect.
Moderate	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low	Any estimate of effect is very uncertain.

Results of Evidence-Based Analysis

Other Systematic Reviews

The Medical Advisory Secretariat evidence review identified 2 previous health technology assessment reports on CXL, both involving management of keratoconus. The first assessment was performed by the National Institute for Health and Clinical Excellence (NICE) in Great Britain in 2009 (36) and the other by the Health Technology Inquiry Service at the Canadian Agency for Drugs and Technologies in Health (CADTH) in 2010. (37) The NICE report reviewed evidence published up to July 2009 for CXL management of KC and identified 11 reports, one involving a RCT. (38) The resulting NICE guideline (39) concluded that there was insufficient high quality information to recommend the procedure for all KC patients and that CXL should only be performed in special circumstances. The CADTH report was a limited literature search on reports published between 2005 and April 2010. Their review identified 8 studies, one being a RCT (38), on the effectiveness of CXL for KC. All studies reported CXL to be an effective treatment for KC.

Medical Advisory Secretariat Systematic Evidence Review

In the Medical Advisory Secretariat review, 65 reports (16 case reports) involving 1403 patients undergoing CXL for management of corneal thinning disorders were identified. The reports, summarized below in Table 6, are grouped according to their primary clinical indication, whether or not secondary procedures were used in conjunction with CXL (referred to as CXL-Plus), (40) and whether or not they were safety-related.

Table 6: Evidence Base for CXL for Corneal Thinning Disorders*

Effectiveness - Keratoconus	Longitudinal Pre-Post Cohorts	6 reports	264 patients
	Comparative Pre-Post Cohorts – Untreated	5 reports	145 patients
	Comparative Pre-Post Cohort – Control Group	1 report	10 patients
	RCT (KC and Post-Lasik ectasia)	1 report	58 patients
Effectiveness- Post-Lasik-Ectasia	Longitudinal Pre-Post Cohorts	4 reports	66 patients
CXL-Plus: (CXL +ICRS)	Longitudinal Pre-Post Cohorts	6 reports	91 patients
CXL-Plus: (CXL + PRK)	Longitudinal Pre-Post Cohorts	8 reports	74 patients
CXL-Plus: (CXL +IOL)	Case Reports	2 reports	12 patients
Safety	Safety and Recovery Series	18 reports	668 patients
	Complication Case reports	14 reports	15 patients

* CXL indicates corneal collagen cross-linking; ICRS, intrastromal corneal ring segment; IOL, intraocular lens implant; PRK, photorefractive keratectomy

The reports are also summarized in Table 7 by type of study design. The reports on treatment outcomes involved pre-post nonrandomized longitudinal cohort follow-up studies. The reports involve several forms of pre-post longitudinal follow-up, ranging from uncontrolled follow-up of only the treated eye, follow-up of both the treated and untreated fellow-eye, and follow-up of the treated eye and an untreated control group. Case reports and case series, particularly for complication events, were included in this review because of the rarity of corneal thinning disorders such as keratoconus.

Table 7: Level of Evidence Summary for CXL Management of Corneal Thinning Disorders*

Study Design	Number of Eligible Studies
RCT Studies	
Systematic review of RCTs	
Large RCT	
Small RCT	4
Observational Studies	
Systematic review of non-RCTs with contemporaneous controls	2
Non-RCT with contemporaneous controls	6
Systematic review of non-RCTs with historical controls	
Non-RCT with historical controls	37
Database, registry, or cross-sectional study	
Case reports	16
Retrospective review, modeling	
Studies presented at an international conference or other sources of grey literature	
Expert opinion	

* RCT indicates randomized controlled trial

The organization of the MAS evidence review follows the evidence grouping laid out in Table 6 and includes the following 4 sections: Section A. Effectiveness of CXL in keratoconus; Section B. Effectiveness of CXL in post-LASIK ectasia; Section C. Adjunct interventions with CXL; and Section D. Safety of CXL.

Section A. Effectiveness of CXL for Keratoconus

Fifteen longitudinal pre-post studies were included, 2 involving serial reports (8;41-43) on the same patient population on the effectiveness of CXL for KC. The summary details of these studies are outlined in Appendix 2, Table A1. Five of the studies (7;41;42;44-46) involved longitudinal follow-up of both the treated eye, (usually the worse eye), and the untreated fellow-eye as a comparator. One study (47) was a 3-arm RCT involving 2 comparator groups, a sham treatment group with riboflavin only, and the untreated fellow-eye.

The studies were conducted mainly in European countries; only one was conducted in North America. (47) The longitudinal follow-up was generally 1 year. Three studies reported longer term follow-up at 2 years (6;7;48) and 4 years. (41) Patients were generally in their twenties and thirties, although in one report involving an Indian cohort (49), the mean patient age was 16.9 years. In all reports, males outnumbered females more than two-fold. The inclusion criteria were consistent. Patients were all reported to have progressive KC, although the definition of progressive KC varied and in some cases was not defined. While most studies reported the degree of KC to be at a mild or moderate stage, 2 studies involved patients at more advanced stages of moderate or severe disease. (7;50) CXL treatment in the reports was highly standardized and there was little deviance from the original Dresden protocol proposed by Wollensak et al. in the first clinical report of CXL. (7) One study, however, deviated from protocol by not removing the central corneal epithelium prior to the irradiation phase. (46) The evaluations of treatment on disease progression, particularly for corneal typography, varied, involving different devices

and different measures such as corneal surface curvatures, asymmetry indices and higher order corneal aberrations.

As the main treatment objective is to stabilize the underlying disease process, corneal topography was considered the key outcome measure. The effects of CXL on corneal topography were reported as keratometry measures (K-value) in diopters (D), which represent the radius of corneal curvature and provide a measure of the cone protrusion. K-values were also reported as mean, minimum (K_1), or maximum (K_2) values. In a comparative study evaluating keratometry values in KC compared to normal eyes, the mean K-value for normal subjects was 43.28± 1.17 D (range 41.53 to 45.40 D) and for KC subjects was 49.29 ± 4.37 D (range 42.97 to 60.33 D). (13) Other authors have indicated a range of increasing K-values reflecting the increasingly severity of KC corneas: mild ≤48 D; moderate 48–53; advanced D > 53 D. (51)

The remodeling effects of CXL on corneal surface topography represented by mean K-values are summarized below in Table 8 for longitudinal pre-post cohort studies involving only the treated eye While Table 9 contains follow-up studies involving both the treated and untreated as a control. All studies, except that by Doors et al. (52), reported disease regression or significant improvement ($P < .05$) of corneal surface topography as measured by keratometry. In the Doors et al. study, the disease did not regress as measured by K-values. However, the K-values did not increase either, suggesting that the disease had stabilized or had not advanced in follow-up. The results for the treated eye compared to the untreated eye are shown in Table 9 and in all cases; the corneal topography of the treated eye was shown to significantly improve whereas the topography of the untreated eye was reported to worsen.

Table 8: Topographic Outcomes in Longitudinal Pre-Post Cohorts after CXL in Treated Eyes*

Author, Year	Patients (eyes) Mean Age ± SD	Keratometry (K)	Pre-post 12 mo Change Mean Diopter ± SD	Pre-post *P* -Value
Agrawal V, 2009 (49)	25 P (37 e) 16.9 ± 3.5 yrs	K-Max K-Apex	-2.47 ± 3.89 D -2.73 ± 7.95 D	0.004 0.004
Arbelaez M, 2009 (50)	19 P (20 e) 24.4 yrs (R 18 to 44)	K- Average K- Apex	-1.36 D -1.40 D	0.004 0.01
Doors M, 2009 (52)	29 P (29 e) 35.1±11.7 yrs	Central K K-Max	0.64 ± 1.73 D - 0.29 ± 2.05 D	> 0 .05 > 0 .05
El-Raggal T, 2009 (53)	9 P (15 e) 26.4 yrs (R 21 to 31)	K-Average K-Max	- 1.50 D -1.75 D	< 0.001 < 0 .001
Raiskup-Wolf F, 2008 (6)	130 P (142 e) 30 ± 10.5 yrs	K-Apex K-Max	-2.68± 7.61 D -1.46 ± 3.76 D	< 0 .01 < 0.01
Saffarian L , 2010 (54)	53 P (92 e) 21.5 ±3.4 yrs	Sim-K	-0.94 ± 0.71 D	< 0 .001

*D indicates diopter; e, eyes; K, keratometry; Max, maximum; Mo, month; P, patients; R, range; SD, standard deviation; Sim, simulated; Yrs, years

Table 9: Topographic Outcomes in Longitudinal Pre-Post Cohorts after CXL in Treated and Untreated Fellow-Eyes*

Author, Year	Patients (eyes) Mean Age	Keratometry (K)	Treated Eye Pre-post 12 Mo Change Mean Diopter ± SD *P* -Value	Untreated Eye Pre-post 12 Mo Change Mean Diopter ± SD
Caporossi A, 2010 (41)	44 Patients (44 e) (R, 10 to 40 yrs)	K-Average	-1.96 ± 0.63 D *P* < 0 .05	+1.2 ± 0.96 D
Henriquez M, 2011 (44)	10 Patients (10 e), 10 control subjects 29.7 (R,15 to 43) yrs	K-Max K- Min	-2.66 D *P* = 0.04 -1.61 D *P* = 0.03	90% (9/10) increased K-Max
Koller T, 2009 (45)	21 Patients (21 e) Age NR	Minimum corneal curvature radius	55.0 to 54.3D *P* = 0 .01	48.6 to 49.2 D P = 0.002
Leccisotti A, 2010 (46)	51 Patients (51 e) 26.9 ± 6.3 yrs	K-Apex Sim-K	- 0.51 ± 7.79 *P* > 0.05 -0.10 ± 1.44 *P* > 0.05	1.61 ± 6.28 D P > 0.05 0.88 ± 2.35 D P > 0.05
Vinciguerra P, 2009 (42)	28 Patients (28 e) (R, 24 to 52 yrs)	K-Min K-Max	46.10 to 40.22 D *P* = 0 .0003 50.37 to 44.21 D *P* = 0.0011	NR
Wollensak G, 2003 (7)	22 Patients (23 e) 31.7 ±11.9	K-Max	2.01 ± 1.74 D *P* = 0.03	NR

*D indicates diopter; e, eyes; K, keratometry; Max, maximum; Mo, month; NR, not reported; R, range; SD, standard deviation; Yrs, years

One RCT trial involved 65 patients with either KC or post-LASIK ectasia cases. (47) The trial was a 3-arm RCT in which control comparisons were made with the untreated fellow-eye and a sham group receiving riboflavin only (crossed over to active treatment at 3 months). In the sham control group (riboflavin only), there were no significant changes in visual acuity (BCVA), refraction (sphere, cylinder), topographic values (K-Max, K-Avg) or corneal astigmatism at 1-month and 3-months follow-up. There were also no significant changes in visual acuity in the fellow untreated eye (BCVA, UCVA) or refraction (cylinder, sphere) at 12-months. Topography in the untreated eyes at 12-months as measured by K-Max [K-Max +0.29 ± 1.19 D (*P* = .19)] and K-Avg [[K-Avg + 0.20 ± 0.79 D (*P* = .18)] had worsened at 12-months, although not significantly. Corneal astigmatism was significantly worse at 1 year (mean change 0.34 ± 0.82D, *P* = .03). For the treated eyes at 12-months, uncorrected distance visual acuity and corrected distance visual acuity [UDVA (*P* = .02) CDVA (*P* < .001)] and topography [K-Max (*P* < .001), K-Avg (*P* < .001)] were significantly improved over the control (untreated eyes).

The effects of CXL on corneal disease progression were also evaluated using advanced corneal wavefront surface aberrometry techniques, including measures of spherical aberration and indices of corneal asymmetry (Table 10). Four studies (41;49;50;52) reported on these measures and 3 others (42;45;46) also reported change comparisons between the treated and untreated fellow-eye (Table 11). These results were more varied than the topographic measures, although the majority of the studies reported significant improvements in lower- and higher-order corneal aberration scores.

Table 10: Impact of CXL on Higher Order Topographic Outcomes*

Author Year	Patients (P) Mean Age± SD	Topographic Measure	Pre-Post Change	*P -Value*
Agrawal V, 2009 (49)	25 P (37 e) 16.9 ± 3.5 years	Corneal wavefront surface aberrometry	Spherical and higher order corneal aberrations did not show significant changes	> 0 .05
		Corneal wavefront surface aberrometry	Coma component (lower order aberrations) showed significant reduction	0.003
Arbelaez M, 2009 (50)	19 P (20 e) 24.4 years (R 18 to 44 yrs)	Corneal wavefront surface aberrometry	Spherical and higher order corneal aberrations did not show significant changes	0.041
		Corneal wavefront surface aberrometry	Absolute RMS and absolute coma were significantly reduced	0.026
Caporossi A, 2010 (41)	44 P (44 e) (R 10 to 40 yrs)	Corneal wavefront surface aberrometry	Total wavefront higher order aberrations were significantly reduced	< 0 .00001
		Surface aberrometry (CSO Eye Top)		
		Corneal symmetry-Inferior-Superior-inferior index (SI)	Pre-post SI asymmetry index significantly improved	< 0.0001
			Spherical aberration remained unchanged	> 0 .05
Doors M, 2009 (52)	29 P (29 e) 35.1 ±11.7 years (R 19 to 76 yrs)	Corneal aberrometry (IRX-3 Wavefront Aberrometer)	Higher-order aberration values coma-x, coma-y and spherical aberration were not significantly changed	> 0.05

*e indicates eyes; Mo, month; Preop, Preoperative; R, range; RMS, root mean square; SD, standard deviation; SI, superior-inferior; Yrs, years

Table 11: Impact of CXL on Higher Order Topographic Outcomes-Comparison of Treated and Untreated Fellow-Eye *

Author Year	Patients (P) Mean Age ± SD	Topographic measure	Treated Eye Pre-Post Change	Untreated Fellow-Eye Pre-Post Change	Treated versus Untreated Pre-Post Change	*P-Value*
Koller T, 2009 (45)	21 P (21 e) Age NR	Corneal topography Pentacam system with Scheimpflug camera –	Rmim/mm 6.14 to 6.21 *P* = 0.01	Rmin/mm 6.94 to 6.86 *P* = 0.002	Rmin/mm 0.066 ± 0.10 vs -0.08 ± 0.10	0.0009
		Minimum corneal curvature radius (Rmin) At 12-months	Rmin/D 55.0 D to 54.3D *P* = 0.01	Rmin/D 48.6 D to 49.2 D *P* = 0.002	Rmin/D -0.62 ± 0.9 D vs 0.57 ± 0.8 D	0.0009
			4 / 7 Pentacam KC indices showed significant improvements towards a more normalized corneal anterior surface			
			Based on Rmin Change 0.12 mm ≈ 1 D	Based on Rmin Change 0.12 mm ≈ 1 D		
			Progressed: N = 0 Unchanged: N = 13 Regressed: N = 8	Progressed: N = 7 Unchanged: N = 14 Regressed: N = 0		
Leccisotti A, 2010 (46)	51 P (51 e) 26.9 ± 6.3 (R 26.9 to 39) years	Corneal surface regularity index (ISV abnormal >37) At 12-months Tangential video keratography (Keratograph)	ISV 76.4 ± 28.2 to 77.3 ± 28.8 Mean change 0.9 ± 4.69 (p > .05)	ISV 48.2 ± 14.3 to 53.5 ± 19.5 Mean change 5.3 ± 7.30 (p > .05)	ISV (95% CI) 1.99 to 6.81	
Vinciguerra P, 2009 (42)	28 P (28 e) R 24 to 52 years	Total (corneal and internal) wavefront analysis performed with Nidek OPD-Scan – 21-Klyce Indices	At 12-months,the Klyce indices had significantly improved (p< .05), 19 of the 21 indices improved, 1 remained the same (IAI), and 1 worsened (Kmin)	At 12-months,the Klyce indices were significantly worse, none of the indices improved, 17 worsened, and 4 remained the same		

Author Year	Patients (P) Mean Age ± SD	Topographic measure	Treated Eye Pre-Post Change	Untreated Fellow-Eye Pre-Post Change	Treated versus Untreated Pre-Post Change	*P-Value*
			In wavefront analysis, total (corneal and internal) aberrations, total higher order aberrations, total astigmatism, total coma, and total spherical aberrations were significantly decreased i.e., improved	In wavefront analysis, total astigmatism and total coma significantly increased, i.e., worsened. No significant change was noted with total, higher order or spherical aberrations		

*D indicates diopter; e, eyes; ISV, deviation of individual corneal radii from mean values; Min, minimum; P, patients; R, range; SD, standard deviation

Refraction

Refractive outcome measures include the refractive sphere (S) and the refractive cylinder (C). Spherical equivalent (SE) is a summary measure of the sphere and the cylinder [SE = S + 0.5 C]. Spherical correction is the amount of power [(in diopters (D)] required in a lens to correct the visual acuity to an acceptable level, usually 20/20. The refractive cylinder, also measured in diopters, is a measure of astigmatism (asymmetries in the corneal curvature). High degrees of astigmatism are normally considered to be ≥ 3 diopters. Refractive changes of one diopter or more are considered clinically significant as they usually require an optical correction. (18)

The impact of CXL on refractive outcome measures for the refractive sphere and refractive cylinder at 12-month follow-up are outlined in Tables 12 and 13 respectively. Reductions in the refractive sphere after CXL were greater than one diopter and significantly improved over baseline in 4 studies. Two studies (42;54) reported refractive sphere improvements that were not significant. These studies, however, also had lower levels of spherical correction at baseline than the others.

Table 12: Change in Refractive Sphere at 12-Months Following CXL for Keratoconus*

Author, Year	Eyes	Mean Refractive Sphere (Mean Diopters ± SD)			
		Preop	Postop	Pre-Post Change	*P - Value*
Agrawal V, 2009 (49)	37	-7.24 ± 4.67 D	NR	1.20 D in 47%	0 .005
Arbelaez M, 2009 (50)	20	-3.84 ± 5.10 D	-2.58 ± 3.22 D	NR	0 .033
Caporossi A, 2006 (41)	44	NR	NR	1.62 ± 1.03 D (R 0 to 3.75 D)	< 0.00001
El-Raggal T, 2009 (53)	15	-3.20 ± 1.46 D	-2.73 ± 1.56 D	NR	< 0 .001
Saffarian L, 2010 (54)	92	-1.06 ± 1.92 D	-0.87 ± 1.60 D	-0.18 ± 0.790 D	> 0 .05
Vinciguerra P, 2009 (42)	28	-1.86 ± 2.58 D	-1.58 ± 2.64 D	NR	> 0 .05

*D indicates diopters; NR, not reported; Preop, preoperative; Postop, postoperative; R, range; SD, standard deviation

Although significant improvements in the refractive cylinder after CXL over baseline (Table 13) were reported in 3 studies, (42;50;54) the effects were more variable and there was less change over baseline than for the refractive sphere.

Table 13: Change in Refractive Cylinder at 12-Months Following CXL for Keratoconus*

Author, Year	Eyes	Mean Refractive Cylinder (Mean Diopters ± SD)			
		Preop	Postop	Pre-Post Change	*P* - Value
Arbelaez M, 2009 (50)	20	-4.04 ± 1.52 D	-2.79 ± 1.13 D	NR	0.0003
Caporossi A, 2006 (41)	44	NR	NR	-0.52 ± 0.38 D R 0.75 to -2.0 D	> 0.05
El-Raggal T, 2009 (53)	15	4.90 ± 0.74 D R 3.75 to 6.0 D	4.95 ± 0.76 D R 4.0 to 6.0 D	NR	0.384
Saffarian L, 2010 (54)	92	-3.93 ± *1.67 D*	-3.14 ± *1.50 D*	0.78 ± *1.49 D*	< 0.001

Author, Year	Eyes	Mean Refractive Cylinder (Mean Diopters ± SD)			
		Preop	Postop	Pre-Post Change	*P* - Value
Vinciguerra P, 2009 (42)	28	-3.02 ± *1.74 D*	-2.76 ± *1.11 D*		< 0.05

*D indicates diopter; NR, not reported; Preop, preoperative; Postop, postoperative; R, range; SD, standard deviation.

Visual Acuity

The impact of CXL on visual acuity is outlined below in Table 14. Although CXL treatment is not intended to improve vision, the induced changes in corneal topography may secondarily result in such improvements. Examining the maintenance or stability of the induced corneal changes and the subsequent improvements in visual acuity also provides an indirect measure of treatment effect on the underlying disease process.

Visual acuity (VA), both uncorrected visual acuity (UCVA) and best-corrected visual acuity (BCVA), was reported in all studies, but in different formats. Snellen VA is the most common measure of VA; in this measure, change in visual acuity (represented as gains of lines of vision) is often used as a measure of treatment effectiveness, whereas loss of lines of vision is considered to be a vision safety concern. Generally, a gain or loss of within 1 line is considered to be within normal variability, representing no change. (18) A gain or loss of ≥ 2 lines is considered a clinically significant gain or loss of visual acuity. A loss of ≥ 2 lines of BCVA is also considered to be a vision safety concern.

The impact of CXL on VA (see Table 14) was variable, with improvements in BCVA of ≥ 1 Snellen line ranging from 27% to 60%. This was balanced with loss of BCVA that ranged from 7% to 10% for a loss of 1 Snellen line or more to 2.9%, for a loss of 2 Snellen lines or more.

Table 14: Impact of CXL on Best Corrected Visual Acuity at 12-Months*

Author, Year	Patients	Improvement BCVA ≥ 1Snellen line	No Change BCVA	Loss BCVA
Koller T, 2009 (55)	105	NR	NR	2.9% (95% CI 0.6% - 8.5%) ≥ 2 Snellen line
Agrawal V, 2009 (49)	37	20 (54%)	10 (28%) Lines Not defined	NR
Arbelaez M, 2009 (50)	20	12 (60%)	8 (40%) Lines Not defined	-
Doors M, 2009 (52)	20	10 (50%)	5 (25%) Lines Not defined	NR
El-Raggal T, 2009 (53)	15	4 (27%)	NR	1 (7%) 1 line
Raiskup-Wolf F, 2008 (6)	142	75 (53%)	29 (20%) Lines Not defined	NR
Hersch P, 2011 (47)	49	22 (45%)	23 (46%) Within 1 Snellen line	4 (10%) 1 Snellen line
Wollensak G, 2003 (7)	22	11 (50%)	9 (41%) Within 1 Snellen line	2 (9%) ≥ 1 Snellen line

Author, Year	Patients	Improvement BCVA ≥ 1Snellen line	No Change BCVA	Loss BCVA
Range		27% - 60%	20% - 46%	2.9% - 10%

*BCVA indicates best corrected visual acuity; CI, confidence interval; NR, not reported; P, patients

Treatment Failure

Table 15 outlines an estimation of treatment failure based on the inability of CXL to stabilize the underlying disease process as measured by corneal topographic outcome measures. Treatment failure, which is indicated by progressive or increasing keratometry maximum values greater than 1 diopter, ranged from 8% to 10% of cases. Treatment success, which occurred in the majority of cases, included cases where corneal topography was improved or stabilized in the first year of follow-up. Estimates of disease regression based on a K-Max threshold of 1 diopter decrease ranged from 37% to 56%. Studies including disease regression values of K-Max decreases of 2 diopters ranged from 35% to 45%. An indirect measure of treatment failure was the degree to which VA was lost in follow-up. Estimates for VA loss reported in Table 14 were consistent with the low rate for worsening corneal topography in similar follow-up periods.

Table 15: Treatment Failure Assessed by Topographic Outcome Measures at 12-Months*

Author, Year	Patients	Regression Decrease K-Max	Stable K-Max	Progression Increase K-Max
Koller T, 2009 (55)	105	39 (37%) > 1 D	58 (55%) ± 1 D	8 (8%) > 1 D
Agrawal V, 2009 (49)	37	20 (54%) > 1 D	14 (38%) ± 0.5 D	3 (8%) > 1 D
Raiskup-Wolf F, 2008 (6)	142	80 (56%) > 1 D	43 (30%) ± 0.5 D	NR
Hersch P, 2011 (47)	49	17 (35%) ≥ 2 D	NR	5 (10%) ≥ 1 D
Wollensak G, 2003 (7)	22	10 (45%) > 2 D 12 (55%) >1 D	8 (36%) ±1.0 D	0
Range		35% - 56%	30% - 55%	8% - 10%

*D indicates diopter; K-Max, maximum keratometry; P, patients

Contact Lens Tolerance Following CXL

Other measures of treatment success, such as the improvement in contact lens tolerance after CXL (or the need for improvement following CXL treatment), were not reported in any of the studies evaluated in this review.

Vision-Related Quality of Life and Patient Satisfaction

Vision-related quality of life or patient satisfaction with vision was not reported in any of the studies evaluated in this review.

Section B. Effectiveness for Post-Lasik Induced Corneal Thinning

Three studies reported on 34 patients undergoing CXL for post-LASIK ectasia. (56-58) The reports are summarized in Table 16. One other report involved the use of both CXL and photorefractive keratectomy

in patients with post-LASIK corneal ectasia. (59) The studies were generally small series involving less than 20 patients with 1-year follow-up. In one report (56), 7 of the 10 patients were diagnosed with forme fruste keratoconus, an undiagnosed earlier disease state of keratoconus prior to LASIK.

In general, there were improvements in corneal topography measured by K-Max, although mean improvements were not statistically significant. The small sample sizes and extreme variability in the outcome measures limit the power of these studies. The report by Hafezi et al. (56) concerning the proportion of patients with significant clinical benefit, measured by corneal topography and subsequent refraction and visual acuity, shows that the majority of patients experienced improvement in the underlying disease in follow-up. The baseline measure of corneal topography in this patient population, however, was significantly higher than those in the other 2 studies.

Table 16: CXL Treatment of Keratectasia After Laser In-Situ Keratomileusis*

Author, Year Patient (eyes) Mean Age	Observation Point	Topography K-Max (Mean Diopter ± SD)	Refractive Sphere (Mean Diopter ± SD)	Refractive Cylinder (Mean Diopter ± SD)	Visual Acuity UCVA (LogMar)	Visual Acuity BCVA (LogMar)
Hafezi F, 2007 (56)						
10 P (10 e) 36.2 years (R; 27 to 43)	Baseline	57.4 D	NR	NR	NR	NR
	12-month Postop	56.3 D 5/10 ↓ ≥ 2 D	7/10 ↓ ≥ 2 D	7/10 ↓ ≥ 2 D	NR	8/10 > 1 line
	P-Value		NR	NR		NR
Salgado J, 2011 (57)						
15 P (22 e) 38.4 years (R; 27 to 51)	Baseline	44.12 ± 3.97 D	-1.15 D	-2.59 D	0.53 ± 0.38	0.19 ± 0.21
	12-month Postop	42.04 ± 2.67 D	-1.06 D	-2.10 D	0.40 ± 0.27	0.15 ± 0.14
	P-value	NS	NS	NS	NS	NS
Vinciguerra P, 2010 (58) 9 P (13 e) 42 years (R; 30 to 59)	Baseline	45.93 ± 6.03 D (R 37.42 to 57.01)	-2.96 ± 2.63 D (R -9.00 to 0.25)	-2.40 ± 2.06 D (R -6.00 to 0.0)	1.08 ± 0.43 (R 0.40 to 1.70)	0.16 ± 0.14 (R 0.00 to 0.40)
	12-Month Postop	42.49 ± 4.88 D (R, 35.49 to 49.12)	-2.25 ± 1.39 D (R, -5.00 to -0.50)	-2.00 ± 2.00 D (R, -5.00 to 0.0)	0.94 ± 0.46 (R 0.01 to 1.30)	0.06 ± 0.08 (R 0.00 to 0.22)
	P-Value	NS	NS	NS	NS	< 0 .05

*e indicates eyes; NS, not significant; NR, not reported; Postop, postoperative; R, range; SD, standard deviation

Section C. Adjunct Interventions with CXL

CXL and Intrastromal Corneal Ring Segments

CXL is not intended to and does not always improve visual acuity, either UCVA or BCVA. Instead, joint approaches have been employed in order to both halt the underlying disease progression and improve visual acuity. The use of joint or adjunct procedures has been referred to as CXL-Plus. (40) Adjunct approaches with CXL involving the use of intrastromal corneal ring segments (ICRS) or the use of surgical refractive procedures such as photorefractive keratectomy (PRK), also referred to as surface laser ablation, have been employed as complementary rather than competitive techniques in order to improve visual acuity.

Six reports (60-65) were identified involving a total of 91 patients with KC who were undergoing adjunct interventions combining ICRS with CXL**.** The summary information on these studies, 3 involving RCTs, is outlined below in Table 17. Three of the studies evaluated the utility and timing or sequencing of ICRS and CXL. The Chan et al. RCT study (66), which evaluated the impact of adding CXL to ICRS compared to ICRS alone, demonstrated that there were additional benefits to the joint approach, with the resulting improvements being greater for corneal topography than for visual acuity.

Two other studies, both RCTs, evaluated different sequences of CXL and ICRS. (61;62) Additional gains for visual acuity were reported for both sequential and simultaneous approaches, although the reduction in mean keratometry was statistically greater with same day procedures. In one study it was reported that performing the 2 procedures simultaneously resulted in a more marked and persistent stromal haze (62), while in the other study a significant decrease in endothelial cell density (61) was noted.

A study by El-Raggal et al. (63) evaluated the effects of CXL performed prior to ICRS on the laser power settings that are needed for ICRS placement. Performing CXL first resulted in greater difficulty with ICRS placement and required the use of higher laser power settings, resulting in a more severe and persistent corneal reaction.

Two studies (64;65) evaluated the effectiveness of ICRS and CXL performed transepithelially (without removing the epithelium). Transepithelial CXL performed 6 months *after* ICRS resulted in additional effects on outcomes. (64) ICRS initially had a significant flattening effect on the cornea, with a decreased K-Max of 1.28D. After CXL, there was an additional flattening of the cornea, with a further decrease in K-Max of 0.76 D. In addition, ICRS significantly decreased myopia with improved refraction (decreasing sphere by 2 D and cylinder by nearly 0.5 D),while after CXL there was an additional reduction in sphere of 0.5 D and in cylinder of 0.15 D. Visual acuity improved by 2 Snellen lines (UCVA, BCVA) after ICRS placement and by an additional 1Snellen line after CXL (UCVA).

Table 17: Adjunct Procedures with CXL Involving Intrastromal Corneal Ring Segments

Author, Year	Patients (eyes)	Study Design	Objective
Chan C, 2007 (60)	21 P (25 e)	Matched case control	To compare ICRS implant versus ICRS and simultaneous CXL
Coskunseven E, 2009 (61)	43 P (48 e)	RCT 2- arm	To compare 2 sequences at 7 month intervals: CXL + ICRS Vs ICRS + CXL
El-Raggal T, 2010 (62)	16 P (10 e)	RCT 2-arm	To compare sequential (ICRS and CXL 6 months postop) or simultaneous order of ICRS then CXL
El-Raggal T, 2011 (63)	11 P (14 e)	RCT 3-arm	To evaluate the effect of CXL on laser channel creation in subsequent ICRS 6 months postop

Author, Year	Patients (eyes)	Study Design	Objective
Ertan A, 2009 (64)	17 P (25 e)	Longitudinal cohort	To evaluate sequential transepithelial CXL 6 months after ICRS
Vicente L, 2010 (65)	10 P (14 e)	Longitudinal cohort	To evaluate simultaneous ICRS and transepithelial CXL

*CXL indicates corneal cross-linking; e, eyes; ICRS, intrastromal corneal ring segments; NS, not significant; NR, not reported; P, patients; postop indicates postoperative

CXL and Photorefractive Keratectomy

Seven studies (4 as case reports) were identified involving 52 patients with KC undergoing CXL and photorefractive keratectomy (PRK). (67-73) One additional report included 32 patients with post-LASIK induced ectasia undergoing simultaneous CXL and PRK. (74) The details of these reports are summarized below in Table 18 and in Appendix 2, Table A3. In general, the purpose of the keratectomy was to smooth the anterior cornea in order to decrease the irregular astigmatism and restore refractive properties of the anterior corneal surface, thereby improving visual rehabilitation.

Table 18: Adjunct Procedures with CXL Involving Photorefractive Keratectomy*

Author	Patients (eyes)	Study Design	Objective
Kanellopoulos A, 2007 (67)	1 P (1 e)	Case report	Effectiveness of sequential topography-guided photorefractive keratectomy with CXL in progressive KC
Kymionis G, 2009 (68)	1 P (2 e)	Case report	Effectiveness of simultaneous photorefractive keratectomy and CXL on progressive pellucid marginal corneal degeneration
Kymionis G, 2010 (70)	1 P (1 e)	Case report	Effectiveness of simultaneous transepithelial phototherapeutic keratectomy and CXL to improve visual outcome in progressive KC
Kymionis G, 2009 (69)	12 P (14 e)	Case series	Effectiveness of simultaneous topography-guided photorefractive keratectomy and CXL for stability and visión improvement in KC
Kymionis G, 2010 (71)	23 P (28 e)	Case series	Effectiveness of simultaneous photorefractive keratectomy and CXL in progressive KC for stability and functional visión
Kymionis G, 2010 (72)	2 P (4 e)	Case reports	Effectiveness of simultaneous conductive keratoplasty and CXL for correction of irregular astigmatism in advanced KC
Stojanovic A, 2010 (73)	12 P (12 e)	Case series	Effectiveness of simultaneous topography-guided transepithelial surface ablation and CXL in KC and pellucid marginal corneal degeneration
Kanellopoulos A, 2011 (74)	22 P (32 e)	Case series	Effectiveness of simultaneous topography-guided partial transepithelial photorefractive keratectomy and CXL in post-LASIK ectasia

*CXL indicates corneal cross-linking; e, eyes; KC indicates keratoconus; P, patients

CXL and Intraocular Lens Implants

The use of intraocular lenses in KC patients following CXL was only reported in 2 studies. (75;76) In the Rodriguez et al. study (76), CXL was performed in a 21-year-old patient with progressive bilateral severe KC. While the first CXL procedure was uneventful, multiple corneal infiltrates and ulceration occurred after the second CXL procedure was performed 11 months later. These symptoms were successfully treated by topical steroids. The residual BCVA of the right and left eyes, however, were 20/50 and 20/30

respectively. Bilateral toric intraocular lens (Staar Surgical) were successfully implanted and BCVA was restored in both eyes to 20/25.

In the Izquierdo et al. study (75), 11 patients with progressive mild to moderate KC underwent CXL, which was followed 6 months later by the implantation of an Artiflex intraocular lens. The Artiflex lens is the foldable version of the Artisan intraocular lens and was chosen because it allows for implantation through a smaller incision, i.e., 3.2-mm incision rather than a 5.2 to 6.2-mm incision used for implanting the Artisian or toric Artisan. In 6 of the 11 patients, BCVA was restored to 20/20; in 1 patient, BCVA improved from 20/30 to 20/25 and in 4 patients, BCVA remained at 20/25. No intraoperative or serious postoperative complications were reported. A mild haze occurred in 2 patients that resolved within 15 days. Endothelial cell density was reported to be decreased (P = .46) over baseline after CXL at 6 months (2759.64 ± 159.84 cells/mm^2 to 2739.09 ± 156.99 cells/mm^2) and statistically deceased (P = .03) after Artiflex implantation at6 months (2668.82 ± 133.17 cells/mm^2).

Section D. Safety

The second objective of this evidence review was to evaluate the safety and complications of CXL. The safety review was based on information from 3 sources: cohort studies evaluating effectiveness; clinical studies evaluating safety, treatment response, or recovery; and published case reports of complications.

Infection

The first step in the CXL procedure involves removing a central region of the epithelial layer to ensure adequate riboflavin penetration of the corneal stroma. A soft contact bandage applied for 4 to 5 days postoperatively is believed to support epithelial regret and the initial stages of stromal rearrangement. (77) Normal epithelial regeneration occurs within the first week of the procedure and generally does so without complication. Creating an epithelial defect, however, can increase the risk for complications such as infection. There can also be further complications if there is an abnormal repair process or delayed re-epithelialization.

Complications such as infection (77-82) and noninfectious keratitis (inflammatory response) (76;83-86) have been reported in case reports involving KC patients undergoing CXL. Two additional reports involved patients undergoing CXL for post-LASIK ectasia. (87;88) The details of these reports are summarized below in Table 19. Infections all occurred within the first week of CXL and most were treated successfully with topical antibiotics and steroids. In one report, the number of patients unaffected was also included yielding a 5.5% (1/18) bacterial infection rate after CXL. (79)

Corneal melting (rapid loss of stromal layer) occurred in 4 case reports (81;83-85), with 3 patients requiring corneal transplants. (81;84;85) The cases involving corneal melt were more likely to be related to conditions of noninfectious keratitis (83-85) rather than infection. (81) The epithelial recovery after CXL involved subtotal epithelialization (81) or total de-epithelialization in 2 cases. (85)

Table 19: Complication Case Reports Following CXL in Keratoconus*

	Complication	Author Year	Case	Organism /agent	Outcome
1	Keratitis noninfectious	Angunawela R, 2009 (83)	40-year-old (NR)	Nonidentified (Sterile infiltrates with overlying epithelial ulceration and corneal melting)	Decreased visual acuity
2	Keratitis noninfectious	Mangioris G, 2010 (86)	25-year-old Female	Nonidentified (Multiple stromal infiltrates)	Decreased visual acuity
3	Keratitis noninfectious	Rodriquez-Ausin P, 2011 (76)	21-year-old (NR)	Nonidentified (Multiple stromal infiltrates)	Placement of Intraocular lens
4	Keratitis noninfectious	Rodriquez-Ausin P, 2011 (76)	11-year-old Male	Nonidentified (Multiple stromal infiltrates)	Decreased visual acuity
5	Diffuse conjunctivitis	Gokhale N, 2010 (84)	19-year-old Male	Nonidentified	Corneal melt /perforation) and corneal transplant
6	Keratitis noninfectious	Labiris G, 2011 (85)	23-year-old Male	Nonidentified	(Corneal melt /perforation) and corneal transplant
7	Keratitis noninfectious	Koppen C, 2009 (89)	28-year-old Female	Nonidentified (Strong ciliary flush and presence stromal white infiltrates)	Residual central and superior scarring with decreased visual acuity
8	Keratitis noninfectious	Koppen C, 2009 (89)	17-year-old Male	Nonidentified (Strong ciliary flush and presence of stromal white infiltrates)	Central scarring led to reduced visual acuity resulting in a corneal transplant
9	Keratitis noninfectious	Koppen C, 2009 (89)	23-year-old Male	Nonidentified (Strong ciliary flush and presence of stromal white infiltrates)	Responded to treatment and initial visual acuity returned
10	Keratitis noninfectious	Koppen C, 2009 (89)	31-year-old Male	Nonidentified (inflammation with corneal edema and infiltrates, irregular epithelium)	Decreased visual acuity

	Complication	Author Year	Case	Organism /agent	Outcome
11	Viral keratitis	Kymionis G, 2007 (78)	21-year-old Female	Herpes simplex	corneal opacity
12	Bacterial keratitis	Perez-Santonja J, 2009 (79)	29-year-old Female	Staphylococcus epidermides	residual haze
13	Bacterial keratitis	Pollhammer M, 2009 (80)	42-year-old (NR)	Escherichia coli	Decreased visual acuity
14	Parasitic keratitis	Rama P, 2009 (81)	32-year-old Male	Acanthamoeba,	corneal melt and corneal transplant
15	Bacterial keratitis	Sharma N, 2010 (82)	19-year-old Female	Pseudomasaeruginosa	Planned keratoplasty
16	Polymicrobiol keratitis	Zamora K, 2009 (77)	32-year-old Male	Streptococcus salivarius, Streptococcus oralis, coagulase-negative Staphylococcus sp.	Residual central corneal stromal haze and subepithelial scar

*NR indicates not reported

Stromal Keratocytes

Several clinical studies involving confocal bio-microscopy (90-92) reported that UVA photo-irradiation in the CXL process depleted the stromal layer of keratocytes. These cells are mainly responsible for the preservation of corneal transparency and mechanical stability, which depend on the synthesis and maintenance of the collagen component and extracellular matrix of the stroma. (93) These studies also reported that the significant cytotoxicity occurring after UVA photo-irradiation appears to be limited to the first 350 µm of the stromal layer and occurs within the first 3 months after CXL. Keratocytes were shown to gradually repopulate and approach normal stromal levels at around 6 months.

Corneal Stromal Haze

Corneal stromal haze is increasingly being recognized as a potential complication after CXL. It has been described as a dust-like change in the corneal stroma or as amid stromal demarcation line between the treated and untreated corneal stroma. (94) Studies reporting corneal haze are outlined in Table 20. Most studies report some degree of corneal stromal haze, usually transitory, following CXL. One study (95) reported a permanent stromal scar in 7% (2/30) of cases. In these cases, due to the location of the scar, there were no adverse effects on vision. A detailed study by Greenstein et al. (94) using quantitative haze measurements to describe trends in haze development and regression reported that although haze decreased between 3- and 12-months postoperatively, it remained elevated over baseline at 12-months.

Table 20: Corneal Stromal Haze after CXL

Author, Year	Haze Occurrence	Finding	Outcome
Caporossi A, 2010 (41)	36% (16/44)	Temporary haze	Resolved with steroids
Doors M, 2009 (52)	0% (0/29)	No corneal haze detected	
Greenstein S, 2010 (94)	44 patients	Haze dosimetry (Scheimpflug) and graded (slit lamp 0 to+4), haze greatest at 1 month, plateaued at 3 months, decreased between 3-and 12-months but still ($p < .001$) elevated at 12-months over baseline	Absolute haze degree associated with poorer vision
El-Raggal T, 2009 (53)	100% (9/9)	All eyes developed faint diffuse stromal haze	Resolved at 1 month
Koller T, 2009 (45)	100% (21/21)	All eyes showed stromal haze at 1 month with a demarcation line in deeper stroma in 18 patients	At 6 months all corneas were clear except in 2 cases with discrete scarring in deep stroma
Lim L, 2011 (95)	7% (2/30)	Permanent deep stromal scar near apical cone away from visual axis	Not affecting vision at this time
Mazzotta C, 2008 (96)	11% (5/44)	Transient corneal opacity similar to haze within first 3 months	Resolved with topical steroids
Vinciguerra P, 2009 (42)	14% (4/28)	Grade +1 haze (Hanna scale)	Regressed after 1 month with topical steroids

Central Corneal Thickness

Measurement of central corneal thinning (CCT) by ultrasound pachymetry provides a direct measure of the impact of CXL on the underlying disease process in KC. Seven studies (41;42;44;50;52;54;97) evaluated CCT by longitudinal ultrasound pachymetry; the results are summarized in Table 21. As expected, the mean baseline CCT values for KC patients were below the normal CCT values, reported to

be 535 µm (95% CI; 473–597). (98) All studies reported decreased CCT values over baseline after CXL at 3 months. Although CCT values continued to improve at the 12-month follow-up mark and to approach baseline values in some studies, they were still significantly reduced at 12-months follow-up in 4 studies. (42;44;52;54)

Table 21: Pachymetry Measures of Central Corneal Thickness in Keratoconus Following CXL*

Author Year	Patients	Baseline CCT (µm) Mean ± SD	3 months CCT(µm) Mean ± SD	Baseline to 3 months CCT (µm)	12-months CCT (µm) Mean ± SD	Baseline to 12-months CCT (µm)	*P*-value Baseline to 12-months
Arbelaez M, 2009 (50)	19	464 ± 27	439 ± 43	-25	464 ± 37	0	> 0.05
Caporossi A, 2010 (41)	44	451	449	- 2	450	-1	> 0 .05
Doors M, 2009 (52)	29	495 ± 48 (R, 427 – 618)	NR	-28 ± 23	NR	-24 ± 19	0.02
Henriquez M, 2011 (44)	10	475	463	- 12	463	-12	0.03
Grewal D, 2009 (97)	102	459 ± 40	436 ± 41	-23	450 ± 51	- 9	0.65
Saffarian L, 2010 (54)	53	461 ± 47 (R, 400 – 576)	NR	NR	445 ± 42 (R, 395 – 570)	-16	< 0.05
Vinciguerra P, 2009 (42)	28	491 ± 31	NR	NR	471 ± 29	-20	< 0.05

*CCT indicates central corneal thickness; R, range; NR, not reported; SD, standard deviation

One study examined variations in CCT during the CXL procedure. (99) Decreases in CCT over baseline (459 ± 22µm) were noted to occur intra-operatively after de-epithelialization (416 ± 21 µm) and after riboflavin installation (341 ± 223 µm [$P < .001$]). In another study, the trend in CCT values was shown to parallel the trend in increased CXL-associated haze occurring after CXL, with a steady decrease in CCT values in the 3 months postprocedure followed by an increase in values over the next 3 months. (100)

Intraocular pressure

The photo-oxidative process of CXL increases the molecular bonds between collagen fibrils, resulting in increased stiffness of the corneal stroma. (28) Several studies investigated whether there was any compensatory or reactive increase in intraocular pressure (IOP) due to this increased corneal stiffness. (6;7;41;52;101-103) The results of these studies are detailed below in Table 22. The study by Goldich et al. (101) was the most extensive measurement of IOP in its use of 3 methods. The Ocular Response Analyzer® is a biomechanical waveform analysis device that provides noncontact IOP measurement through Goldmann-correlated IOP (IOPg) and corneal compensated IOP (IOPcc)**.** Intraocular pressure involving direct or contact measurement was measured using Goldman applanation tonometry (GAT-IOP). In the Goldich et al. study, all 3 measurements showed significantly increased IOP measures over baseline at 1 week and 1 month postoperatively. At 6 months, however, IOP values were still elevated—although not significantly—according to all 3 measures. The other study (103) using the Ocular Response Analyzer did not report increased IOP after CXL. Of the 6 studies evaluating changes in IOP using Goldman applanation tonometry, one study (102) found significant increases at 6-and 12-months following CXL.

Table 22: Change in Intraocular Pressure Following CXL*

Author, Year Patients	Observation Point	GAT-IOP Mean ± SD mm/HG	IOPcc – ORC Mean ± SD mm/HG	IOPg-ORC Mean ± SD mm/HG
Goldich Y, 2009 (101) 10 P	Baseline	13.6 ± 2.06	10.2 ± 1.63	10.1 ± 1.66
	1 week Postop	16.7 ± 2.40 (*P* = .01)	14.1 ± 2.21 (*P* < 0 .001)	14.2 ± 2.73 (*P* < 0 .001)
	1-month Postop	16.5 ± 3.57 (*P* =.04)	13.2 ± 3.55 (*P* = 0.03)	13.5 ± 3.12 (*P* = 0.01)
	3-months Postop	15.3 ± 3.48 *P* =.19)	11.6 ± 3.17 (*P* = 0.023)	12.0 ± 1.25 (*P* = 0.01)
	6-months Postop	14.7 ± 2.87 (*P* = .21)	11.2 ± 2.89 (*P* = 0.33)	12.2 ± 1.14 (*P* = 0.16)
Sedaghat M, 2010 (103) 51 P	Baseline	ND	13.98 ± 2.9	10.47 ± 10.07
	6-months Postop	ND	13.14 ± 2.8 (*P* = 0.027)	10.07 ± 3.0 (*P* = 0.281)
Caporossi A, 2010 (41) 44 P	Baseline	14.773 ± 1.696 (R, 11 to 18)	ND	ND
	6-months Postop	14.795 (*P* > .05)		
	12-months Postop	14.932 *(P* > .05)		
Doors M, 2009 (52) 29 P	Baseline	11.9 ± 3.5 (R, 7 to 20)↑	ND	ND
	1,3,6 and 12-months Postop	NS (values not reported)		
Raiskup-Wolf, F, 2008 (6) 130 P	Baseline change at 12-months Postop	0.2 ± 1.4 (*P* > .05)	ND	ND
Wollensak G, 2003 (7) 22 P	Baseline	13.6 ± 2.0	ND	ND
	Last follow-up	13.8 ± 2.5 (*P* = .612)		
Kymionis G, 2010 (102) 55 P	Baseline	9.95 ± 3.01 (R, 5 to 19)	ND	ND
	6-months Postop	11.40 ± 2.89 (*P* < .001) (R, 7 to 19)		
	12-months Postop	11.35 ± 3.38 (*P* < .001) (R, 6 to 25)		

*ND indicates not done; GAT, Goldman applanation tonometry; IOP, intraocular pressure; ORC, ocular response analyzer; P, patients; R, range; SD, standard deviation

Endothelial Cell Density

Other critical cells potentially at risk from exposure to corneal irradiation are the endothelial cells. These cells, unlike the keratocytes, do not regenerate, and loss of endothelial cells could potentially compromise the ability of the endothelial cell layer to regulate fluid levels in the cornea. Seven studies (7;41;42;44;46;52;99) evaluated the impact of CXL on endothelial cell loss in KC patients. An additional study (58) evaluated the impact on endothelial cell loss in patients undergoing CXL for corneal ectasia post-LASIK. A summary of the study results is outlined in Table 23. Endothelial cell density (ECD) was reported to have decreased—although not significantly—in most of the studies. In these studies, the ECD losses after CXL in KC patients reportedly ranged from an annual loss of 2% to 3.3%. The ECD loss reported for patients with post-LASIK ectasia undergoing CXL was greater than that for KC patients, but was not significantly lower than their baseline.

Table 23: Impact of CXL on Endothelial Cell Density*

Author Year	Patients	Preop cells/mm^2 Mean ± SD	Postop cells/mm^2 Mean ± SD	Pre-Post Change	*P*-Value
Kymionis G, 2009 (99)	15	2780 ± 197	2713 ± 116	- 2.4% at 1 month	0.14
Caporossi A, 2010 (41)	44	2451 ± 130 (R, 2092 to 3016)	2444 R (nr)	-2.0% at 12-months	> 0.05
Doors M, 2009 (52)	29	2701± 352 (R, 2071 to 3803)	2703 ± 273	unchanged	> 0.05
Henriquez M, 2011 (44)	10	2566	2464 at 6 months, 2484 at 12-months	- 3.3% at 12-months	> 0.05
Leccisotti A, 2010 (46)	51	2765 ± 176	2792 ± 146	+ at 6-months	> 0.05
Vinciguerra P, 2009 (42)	28	2651 ± 321	2598 ± 564	-2.0% at 12-months	0.13
Wollensak G, 2003 (7)	22	NR	NR	unchanged	0.45
Vinciguerra P, 2009 (42)	9	2555 ± 470 R(1515 to 2994)	2120 ± 517 R(1547 to 2857)	- 17% at 12-months	> 0.05

*NR indicates not reported; R, range; SD, standard deviation

Other Critical Ocular Structures

Six studies (44;90;92;97;104;105) evaluated other critical structures at risk from ultraviolet-A rays after CXL (see Table 24). The impact of CXL on the retina was evaluated in 2 studies, one using optical coherence tomography (44) and one using Scheimpflug imaging. (97) In the Henriquez et al. study, there was decreased macular thickness over baseline that was not statistically significant throughout the first year**.** (44) The examination using Scheimpflug imaging reported reduced foveal thickness over baseline

that was not statistically significant and there was no change in retinal nerve fiber layer or lens density. (97) No damage to the limbal region was reported in a confocal microscopic evaluation. (92)

In 4 studies following recovery after CXL using in-vivo confocal microscopy examinations, a complete disappearance of subepithelial plexus and anterior midstromal nerve fibers was reported. (90;92;104;105) Nerve regeneration and recovery with normal corneal sensitivity, however, was also noted at around 6 months following CXL.

Table 24: Impact of CXL on Critical Ocular Structures*

Author, Year	Patients	Ocular Structure	Findings
Henriquez M, 2011 (44)	10	Macular thickness	By optical coherence tomography – decreased thickness compared to baseline (216 µm) at 1, 3, 6 and 12-months 191 µm, 191µm, 198 µm and 200 µm
Grewel D, 2009 (97)	102	Lens density	By Scheimpflug imaging – no change in lens density (8.7 µm to 8.7 µm]
		Retinal nerve fiber layer	By Scheimpflug imaging – no change in retinal nerve fiber layer (101 µm to 103 µm)
		Foveal thickness	By Scheimpflug imaging – decreased foveal thickness NS – change from baseline to 12-months 175.7 ± 35.6 µm to 146.4 ± 8.5 µm
Knappe S, 2011 (104)	8	Junction region between Bowman's membrane and the sub-basal nerve plexus	By confocal microscopy the preoperatively tortuous and branched nerve fiber pattern of the sub-basal nerve plexus typical of KC could not be visualized in the central cornea immediately postoperatively and at 3-months postoperatively. At 4 months, the sub-basal nerve fibers again became visible on confocal microscopy.
Kymionis G, 2009 (90)	10	Subepithelial nerve plexus	By confocal microscopy– subepithelial nerve plexus absent at 1 month and regenerated between 3 to 6 months
Mazzotta C, 2006 (105)	10	Subepithelial stromal nerve fibers	By confocal microscopy – normal regeneration and morphological structure of corneal epithelium after 5 days, complete absence of nerve fibers 15 to 30 days post with regeneration continuing and restoring corneal sensitivity after 6 months. No evidence of altered corneal transparency.
Mazzotta C, 2008 (92)	40	Limbus	By confocal microscopy- no damage to the limbal region
		Epithelial nerve plexus	By confocal microscopy, disappearance of subepithelial plexus and anterior-midstromal nerve fibers, restored around 6 months
		Epithelial layer	By confocal microscopy, epithelial regrowth completed after 4 days

*KC indicates keratoconus; NS, not significant

Quality of the Evidence

Table 25 summarizes the quality of evidence for CXL management of corneal thinning disorders, mainly keratoconus, according to the GRADE quality of evidence criteria. (35) Evidence for the impact of CXL on corneal topography, refractive effects and visual acuity, were rated at a moderate level based on several considerations. The studies were prospectively designed as pre-post longitudinal cohort studies involving similar selection criteria and standardized treatment protocols. Several studies also evaluated parallel changes in the untreated as a control comparison to the treated eye, usually the worse eye.

Outcomes were evaluated by comparing standardized outcome measurements with clinically and functionally defined normal ranges. The results in corneal remodeling, refraction, and visual acuity were consistent across clinical studies and involved statistically significant and clinically relevant improvements. Evidence concerning durability, vision-related quality of life, and patient satisfaction was infrequently reported or not yet evaluated. The follow-up in the longitudinal studies—usually one or 2 years at most—was insufficient in determining durability of the treatment effectiveness or the longer-term impact of CXL in delaying or deferring the need for corneal transplants.

Table 25: GRADE Quality of Evidence for CXL of Keratoconus*

Outcome	Design	Quality	Consistency	Directness Appropriate Range of Patients	Other† Modifying Factors	Overall Quality
Safety	Case reports, observational longitudinal pre-post study, comparative pre-post studies (treated to untreated fellow-eye) and 1 RCT	Moderate	Low complication rates reported	Inception cohorts specified with appropriate range		Moderate
Corneal Topography	Observational longitudinal pre-post study, comparative pre-post studies (treated to untreated fellow-eye) and 1 RCT	Moderate	Clinically relevant and statistically significant improvements in treated eye and regression in untreated fellow-eyes	Inception cohorts specified with appropriate range		Moderate
Visual Acuity	Observational longitudinal pre-post study, comparative pre-post studies (treated to untreated fellow-eye) and 1 RCT	Moderate	Clinically relevant and statistically significant improvements, although less predictable than topography	Inception cohorts specified with appropriate range		Moderate
Durability	Observational longitudinal pre-post study	Low	Limited data beyond 2-year follow-up	Inception cohorts specified with appropriate range		Low

*RCT indicates randomized controlled trial
†Studies involving comparisons with untreated fellow-eyes demonstrated significant improvements in the treated eye compared to worsening of the underlying fellow-eye in 1-year follow-up. The treated eye was also the worst eye. Treated patients had progressive keratoconus and given the disease's natural history would not be expected to recover or improve without treatment. Outcomes were based on standardized validated measurements. Estimates of natural variability or normal ranges exist. Improvements in topography were large, clinically relevant, and statistically significant.

Discussion

Collagen cross-linking is a new technique that uses photopolymerization, a combined action of photosensitizing substance (riboflavin) and ultraviolet-A rays (UVA) to increase the rigidity of the

underlying corneal stroma. Currently, CXL is the only treatment available for corneal thinning disorders that targets the underlying disease process. In the last couple of years there has been a significant increase in the number of publications in this area.

This evidence-based review focused primarily on evaluating the safety and effectiveness of CXL for corneal thinning diseases. The principal treatment objective of CXL is stabilizing the underlying disease progression of corneal thinning by increasing collagen bonds in the stromal layer, thereby improving the corneal topography. These changes may also result in improved refraction or vision. In addition, the corneal surface changes may lead to an increased tolerance of contact lenses, thereby reducing refractive error and improving visual acuity. The effectiveness of CXL can therefore be evaluated by various outcome measures and in published longitudinal studies a diverse range of outcomes were evaluated at baseline and follow-up after CXL.

Effectiveness

Overall, 17 longitudinal clinical studies involving more than 500 patients undergoing CXL were identified in this review. The majority of the studies evaluating the effectiveness of CXL have focused on patients with progressive KC. The outcomes reported across trials were consistent and involved statistically and clinically significant improvements in corneal topography and refraction. In almost all the cases, the underlying disease progression, as measured by corneal surface topography, was either halted or reversed. As KC is a chronic progressive disease condition rather than a relapsing disease process, baseline values were unlikely to have improved or have sustained improvement over follow-up without an intervention. Some of the longitudinal studies also involved parallel comparisons with untreated s. In treated eyes, corneal topography stabilized or improved whereas in untreated s, corneal topography continued to worsen. One of the studies was a 3-arm RCT involving control comparisons with a sham treatment group as well as with untreated fellow-eyes. At 12-months follow-up, all outcomes were significantly better in the treated eyes than in the control groups.

Several clinical trials also evaluated the effectiveness of CXL in treating corneal thinning following refractive surgery. Corneal thinning is potentially a major complication following refractive surgery such as LASIK and can occur in several ways. The removal of corneal tissue and the creation of a flap in the LASIK procedure may have a destabilizing effect on the corneal stroma, or the surgery may have been performed in patients with undetected or subclinical forms of KC. The incidence of this complication has been estimated to be between 0.04% and 0.6%. (106) Corneal thinning after LASIK, however, follows a deteriorating visual pattern similar to that of KC, involving increasing myopia and astigmatism, loss of visual acuity, and in some cases, resulting in the need for corneal transplantation.

There were fewer clinical studies—only 4 reports—involving CXL for post-refractive surgery ectasia. Generally, patients with post-refractive ectasia experienced benefits of improved corneal topography similar to those of patients with KC. Although these studies also involved longitudinal pre-post studies, they tended to be small case series and case reports. The studies also differed in that they involved CXL treatment for selected patients, i.e., those experiencing complications from an earlier elective procedure that was often performed at different institutions. One study (56) also reported a number of patients who underwent refractive surgery and developed corneal thinning post-treatment who had been at undiagnosed early stages of KC, thus demonstrating the difficulty of detecting early stages KC in patients undergoing refractive surgery.

Limitations in Effectiveness Research

Research studying the effectiveness of CXL has several limitations. Although a broad range of outcome measures after CXL—including corneal topography, refraction, and visual acuity—were reported, other

important outcomes were not. A secondary treatment objective for CXL, after improvements in corneal topography, would be improvements in contact lens tolerability, if it was required. Neither the effect of CXL on contact lens tolerance nor other outcomes, such as patients' satisfaction with their treatment or with their vision quality, were reported in any of the studies.

Although improvements in corneal outcome measures noted at early follow-up were maintained at 1- and 2-year follow-up, there were only a few longer-term studies and these were based on small numbers of the original cohort. Follow-up in the studies was therefore generally inadequate for evaluating the longer-term success of the treatment. Also, with a collagen turnover in the cornea of several years (105;107), it is uncertain whether CXL is a permanent or temporary treatment and if repeat procedures are needed, whether or not they would be effective. Ultimately, it is uncertain how long CXL will delay or defer the need for a corneal transplant, but given that patients with KC are often young—in their twenties and thirties—a procedure that enables the delaying of transplants for any number of years may still be a valuable option.

Use of Adjunct Therapies with CXL

Corneal cross-linking is mainly intended to stabilize the underlying disease; its impact on refraction and visual acuity are less dependable. In some KC cases, particularly those with high degrees of astigmatism, there was residual refractive error and visual acuity was not restored to functional levels or was unsatisfactory to patients. This has led to attempts to add other interventions to CXL in order to both stabilize the underlying disease and improve visual acuity. Additional or adjunct interventions have included the use of intrastromal corneal ring segments, various surgical refractive approaches, and the use of intraocular lens implants. An emerging issue is therefore the role and utility of adjunct procedures in the treatment of corneal thinning disorders.

Evidence about CXL and adjunct procedures is gradually growing. Six studies—3 involving RCTs—investigated the utility of adjunct interventions involving intracorneal rings. In these studies, the research questions focused on whether or not the procedures act synergistically and, if so, on what outcomes and whether or not the treatment order (concurrently or consecutively) affected these outcomes. Although additional gains were reported after joint interventions, the studies were small and focused on different research questions and outcomes.

Adjunct interventions with intracorneal rings were also employed to determine if the disadvantages of CXL, such as the need for epithelial abrasion, with its attendant pain and delayed recovery, could be avoided. The addition of intracorneal rings concurrently or consecutively with CXL performed without epithelial abrasion was evaluated in 2 small studies. As there was no comparison group involving CXL *with* epithelial abrasion, it is not possible to determine if outcomes were better or worse without epithelial abrasion. Also, there was some suggestion that the use of 2 interventions, although associated with additional benefits, was in some cases also associated with increased risk. In one study (62), there was a report of more marked and persistent stromal haze and in another study (61); joint interventions resulted in a statistically significant reduction in endothelial cells.

A number of studies reported different refractive surgical approaches along with CXL. In these studies, refractive surgeries—typically involving laser ablation techniques intended to "smooth out" corneal surfaces—were performed prior to CXL. Largely case reports and small case series, the studies mainly involved patients with progressive KC, although one large series involved patients with post-LASIK ectasia. The results in these selected cases were difficult to evaluate for without comparison groups it was uncertain to what extent the same outcomes would have been achieved with CXL alone.

Intraocular lens implants have been reported to correct high astigmatism and myopia present in KC patients. They have also been used in conjunction with intracorneal rings in order to improve residual myopia following ring placement in KC patients. (108-110) Regarding KC patients undergoing CXL, there have only been 2 reports involving the use of intraocular lenses to improve visual acuity. Therefore, evidence about the effectiveness of intraocular lenses after either ICRS or CXL has only been documented in case reports. Determining which patients might benefit from intraocular lenses and from which type of lens, is not well defined and is decided on a case-by-case basis.

Safety

Although CXL is a relatively simple procedure, the potential for complications should not be underestimated. Potential risks, however, have to be evaluated in the context of progressive disease and the likelihood—if there is no treatment—of further impaired vision. (111) The safety of CXL was the main issue from the start of this review for several reasons.

First, "the use of UVA radiation and riboflavin have not been applied in the tissue engineering of isolated collagen structures." (112) Second, the procedural parameters of CXL have been tightly defined to minimize the exposure of critical eye structures, such as the lens, limbus, endothelium, and deeper ocular structures— such as the retina— to irradiation and the photo-oxidative process. The radiant exposures, transmissions and damage thresholds for a human cornea after 30 minutes of riboflavin and exposure to ultraviolet irradiation have been established. (113) Although the corneal surface total dose or total dose density with a UVA wavelength of 370 μm and an irradiance of 3mW/cm^2 corresponds to a total dose of 3.4 joules or a total dose density or 5.4 J/cm^2, the radiant exposure to the endothelium and to the deeper corneal structures (lens, retina) is less than 0.25 J/cm^2, well within the recommended safety threshold radiant exposure of 1 J/cm^2 established by the International Commission on Ionizing Radiation Protection. (114)

In addition to study procedural protocols, according to eligibility criteria, patients must have an adequate central corneal thickness—usually, a minimum of 400 microns is recommended—to avoid ultraviolet damage to deeper structures. (28;111;113) This (an adequate central corneal thickness) was also a stated study inclusion criteria in all of the effectiveness cohort studies included in this evidence review. In addition, the published requirements for riboflavin stromal concentration, corneal treatment zone, ultraviolet wavelength source, duration, and delivery were all specified in trials.

Infection and Inflammation

In evaluating safety, it is also recognized that some complications are side-effects related to the procedure itself. The first step in the procedure—involving corneal abrasion to ensure adequate penetration of riboflavin into the stromal layer—increases several risks. For example, with the corneal protective barrier removed there is an increased risk of opportunistic infection. In addition, the use of both steroids and nonsteroidal anti-inflammatory drugs (NSAIDs) after the procedure may exacerbate an infection, particularly in the presence of a delayed epithelial defect and hypoxic conditions produced by a soft-bandage contact lens. The epithelial layer has been generally shown to regenerate within a week (92;105) but when this does not occur, or when it occurs in a delayed or irregular manner, there are further potential risks.

Corneal infections and inflammation were reported to occur after CXL, largely in case reports. They also tended to occur within the first week after the procedure and generally responded to antibiotics. Although there were case reports involving infections, delayed epithelial healing, and corneal melting, which resulted in the need for corneal transplants, these conditions appear to be rare and were not reported in any of the longitudinal cohort reports. Keratitis or generalized inflammatory responses that were not associated with any bacterial or viral infections were also reported. In one study, which included the

number of unaffected patients, a 3.4% (4/117) occurrence rate was reported. Both infectious and noninfectious keratitis, however, can potentially affect vision adversely, although overall estimates of occurrence are uncertain because of variable and limited reporting.

Keratocyte Cytotoxicity

The target of the CXL process is the middle and anterior corneal stromal layers. In addition to strengthening the collagen bonds in these layers, however, the photo-oxidative process may have unanticipated cytotoxic side effects. Several studies (90-92) employing in-vivo microscopic investigations after CXL demonstrated that the corneal stroma layer up to 300 µm was depleted of keratocytes, although it was also reported that the keratocytes gradually repopulated between the third and sixth month follow-up.

Central Corneal Thickness

Central corneal thickness, one of the features of KC, is a key outcome measure for KC treatments. However, most of the studies reported no change in CCT after CXL and, unexpectedly, some studies reported decreases. In one study evaluating intra-operative changes in CCT, decreases were noted to occur immediately after the epithelial removal and values continued to decrease throughout the CXL process. Although CCT was reported to steadily increase in the 6-month follow-up period, in some studies it had not recovered to baseline values at 1-year follow-up. It is uncertain whether this decrease is related to the stromal keratocyte depletion or whether it represents a packing or denser arrangement in the stromal layers as a result of the increased collagen bonding that occurs during CXL.

Haze

Corneal stromal haze was variably defined and reported in almost all of the cohort studies. It was often noted to occur as a mist-like appearance or as a scar in the demarcation line between the treated and untreated corneal stroma. In most cases, it occurred within the first few months, paralleling the periods of keratocyte destruction and CCT decreases. The haze was reported to disappear either spontaneously or with steroid treatment. Depending on degree and location, irreversible stromal haze or scarring can affect visual acuity in several ways. For example, haze located centrally on the visual axis may compromise visual acuity and scarring may increase astigmatism further, adversely affecting refraction and visual acuity. The complication of reduced visual acuity following irreversible haze was reported in a few case reports.

The cause of CXL-associated haze is unknown but several explanations, potentially involving multiple pathways for the pathophysiology of haze, have been suggested. (94) Haze may be an inflammatory response to de-epithelialization or a response to the keratocyte destruction in the anterior corneal stroma. The CXL-induced “packing” changes in the stromal lamellar arrangement and spacing may lead to increased light scatter and decreases in transparency. Or the scarring response may be due to a sublethal effect of the lower UVA dose in the deeper stroma, resulting in fibroblastic transformation and an aberrant scarring response. (95)

Intraocular Pressure

Several studies investigated intraocular pressure (IOP) changes in patients undergoing CXL in order to determine if the stiffening effects and increased corneal rigidity created by CXL produced stroma swelling or increased IOP. Intraoperative pressure, evaluated by both direct and indirect measures that involved noncontact, was reported to have increased postoperatively, usually at the 1- and 3-month follow-up points. In all studies except one, the values had returned to baseline at 12-months follow-up. The relationship between ocular characteristics and the various measurement tonometers, however, is complex and measurement is problematic. In patients undergoing CXL, the measurement of IOP, particularly with contact measurement such as the standard Goldman applanation tonometry, is especially complicated as these measures are affected by corneal curvature and CCT (103), both of which are altered

during CXL. Therefore, it is uncertain whether or not reported IOP increases were the result of an overestimation attributable to corneal changes or were true increases**.**

Critical Structures

A requirement in the CXL treatment process is that UVA irradiation be targeted mainly at the middle stromal layer and that exposure of the deeper layers and other critical ocular structure to UVA be minimized. Inadvertent irradiation exposure of corneal endothelial cells—the deepest corneal cell layer—would be a concern because these cells do not regenerate and any adverse affects or interference in their function could result in corneal edema and swelling. Most studies evaluating endothelial cell density after CXL reported decreased endothelial cell densities at 12-months follow-up that were not statistically significant. The mean annual decreases in cell density, however, ranged from 2% to 3.3% cells/ mm^2 and were higher than the 0.65% ± 0.5% cells/mm^2 normal annual endothelial cell density loss. (115) Although any loss of endothelial cells after a procedure is a concern, the mean cell density counts ranging from 2444 to 2792 cells/mm^2 reported at 1-year follow-up in KC patients were still well above a threshold value of 700 cells/mm^2,which is generally accepted to be associated with an increased risk of corneal edema. (116)

The impact of CXL on other critical ocular structures, such as the retina, was systematically evaluated in 6microscopic confocal in-vivo investigations. This investigative technique enables corneal structures to be visualized rapidly and reproducibly (104) and the results of these studies were remarkably consistent. The studies all reported that although nerve fibers in the stroma had completely disappeared after CXL, regeneration and recovery occurred around 6 months. No damages or changes in the retina or limbal regions were noted.

Conclusions

Corneal collagen cross-linking effectively stabilizes the underlying disease corneal thinning disorders such as keratoconus, and in some cases reverses disease progression as measured by key corneal topographic and refractive outcome measures. However, information on the durability of CXL is limited and it is therefore uncertain whether or not CXL is a temporary or a permanent treatment. Currently, CXL is the only treatment aimed at stabilizing the underlying disease process and it therefore provides a useful alternative to corneal transplant for patients with progressive corneal thinning disorders.

The effects of CXL on visual acuity, however, are less predictable and adjunct interventions such as intrastromal corneal rings, refractive surgeries, and intraocular lens implants are increasingly being employed to restore visual acuity. Although the use of adjunct interventions have been shown to result in additional clinical benefit, the order, timing, and risks of performing adjunctive interventions have not been well established.

Although there is the potential for serious adverse events with CXL, there have been few reported complications in the literature. Reported complications have tended to be related to side effects of the photochemical reactions induced in the CXL process, and these effects were generally reversible. However, to ensure the safety and effectiveness of CXL, strict adherence to standardized CXL procedural protocols is essential.

Economic Analysis

DISCLAIMER: The Medical Advisory Secretariat uses a standardized costing method for its economic analyses of interventions. The main cost categories and the associated methods from the province's perspective are as follows.

Hospital: Ontario Case Costing Initiative cost data are used for in-hospital stay, emergency visit, and day procedure costs for the designated International Classification of Diseases (ICD) diagnosis codes and Canadian Classification of Health Interventions procedure codes. Adjustments may be required to reflect accuracy in estimated costs of the diagnoses and procedures under consideration. Due to the difficulties of estimating indirect costs in hospitals associated with a particular diagnosis or procedure, the secretariat normally defaults to considering direct treatment costs only.

Nonhospital: These include physician services costs obtained from the Ontario Schedule of Benefits, laboratory fees from the Ontario Schedule of Laboratory Fees, drug costs from the Ontario Drug Benefit Formulary, and device costs from the perspective of local health care institutions whenever possible or its manufacturer.

Discounting: For cost-effectiveness analyses, a discount rate of 5% is applied as recommended by economic guidelines.

Downstream costs: All numbers reported are based on assumptions on population trends (i.e., incidence, prevalence and mortality rates), time horizon, resource utilization, patient compliance, healthcare patterns, market trends (i.e., rates of intervention uptake or trends in current programs in place in the Province), and estimates on funding and prices. These numbers may or may not be realized by the system or individual institutions and are often based on evidence from the medical literature, standard listing references and educated hypotheses from expert panels. In cases where a deviation from this standard is used, an explanation is offered as to the reasons, the assumptions, and the revised approach. The economic analysis represents ***an estimate only***, based on the assumptions and costing methods that have been explicitly stated above. These estimates will change if different assumptions and costing methods are applied to the analysis.

Study Question

The objective of this economic analysis was to report on the costs associated with providing corneal collagen cross-linking for patients in Ontario diagnosed with keratoconus.

Economic Literature Review

A literature search was performed on March 3, 2011 using OVID MEDLINE, MEDLINE In-Process and Other Non-Indexed Citations, OVID EMBASE, Wiley Cochrane, CINAHL, and the Centre for Reviews and Disseminationfor studies published from 1948 to April week 3, 2011 for MEDLINE; and from 1947 to week 17, 2011 for EMBASE. Included studies were those with full economic evaluations describing both costs and consequences of ultraviolet-A (UVA) with riboflavin collagen cross-linking therapy (CXL) for keratoconus. The set of search keywords was the same as that used for the clinical systematic review.

According to the clinical systematic review, no health economic evaluations comparing the relative cost-effectiveness of CXL for keratoconus patients were found.

Ontario-Based Cost Impact Analysis

Based on the literature review, the annual prevalence and incidence rates of keratoconus in Ontario were estimated at 54 per 100,000 population (0.0545%) and 2 per 100,000 population (0.0020%), respectively. (16) According to consultation with clinical experts, the number of keratoconus cases eligible for CXL therapy was estimated as follows: approximately 80% of keratoconus patients under 25 years of age and about 45% of patients 25 years of age or older were considered eligible. These rates taken together imply an average annual prevalence of 4,047 cases with an associated incidence (new cases) of about 148 cases per year.

The costs associated with providing CXL therapy to keratoconus patients include the acquisition cost of the UVA (UVX) device and associated physician costs of initial diagnosis, procedure/administration of CXL, and post-procedural follow-up. These costs were estimated through consultation with industry and clinical experts. As CXL is not currently a publicly insured medical service in Ontario, volumes or costs are not publicly reported. To obtain an average cost per patient for the UVA device, it was assumed that all keratoconus patients in Ontario in fiscal year 2011 were treated using one the 15 devices currently available in the province. Current costs associated with the device include approximately $25,000 – $33,000 for the device itself and $8,000 for the device stand and annual maintenance costs. The result is approximately $122 per patient. This cost per patient assumes all capital costs of purchasing the equipment occurred in a given year (i.e., unamortized); while an amortized device would result in a lower cost per patient (per year), the larger estimate was used in the current cost analysis.

Physician costs for keratoconus diagnosis and CXL treatment are shown in Table 26. Costs were divided into preoperative, CXL procedure, and postoperative treatment phases, with June 1, 2011 Ontario Schedule of Benefits (OSB) fees being reported where available. (117) Note that the fee code associated with corneal topography was modified according to expert opinion for the indication of keratoconus specifically; that several procedure fee codes were substituted as CXL is not currently a publicly insured service; and, that drug costs were estimated through consultation with hospital pharmacies. Also note that a clinic cost was included for the CXL procedure based on the general "Operating Room" functional centre indirect costs (i.e., overhead expenses relating to administration, finance, human resources, plant operations, etc.), as reported by the Ontario Case Costing Initiative for corneal transplant patients for keratoconus (i.e., Canadian Classification of Health Interventions code of 1.CC.85.LA, and the Canadian revision of the International Statistical Classification of Diseases code H18.6). (118-120) The final costs per patient were calculated as being $1,036 for the treatment of one eye, or $1,751 for the treatment of both eyes.

The total annual estimated costs of providing CXL treatment to keratoconus patients in Ontario are reported in Table 27. Note that the costs estimated for prevalent keratoconus cases were distributed over 3 years to approximate a phasing-in of the CXL procedure; the average annual cost shown is estimated for the next 3 fiscal years in Ontario. Total costs are further classified according to physician, clinic and medication cost groups, where it is reported that approximately $2.1 million would be spent annually, with physician costs making up about 61% of the total costs (i.e., about $1.3 million annually).

Table 26: Physician and Clinic Costs Associated with CXL Therapy for Keratoconus in Ontario

Clinical phase	Item	Cost
Preoperative		
Ophthalmologist consultation	OHIP fee A235 - Consultation	$71.30
Ophthalmologist repeat visit	OHIP fee A234 - Partial assessment	$25.10
Corneal topography	First visit measurement	$50.00
	Second visit measurement	$50.00
	Total cost	$196.40
CXL Procedure		
Medication	Proparacaine 0.5% - local anaesthesia *	$23.76
	Riboflavin 0.1% - every 2-3 min. for 30 min. *	$19.50
Technical	UV-X Illumination device (UVA irradiation) *	$122.32
	General surgical and technical (disposables, technician) *	$149.00
Ophthalmologist procedure	Professional fee - substitute OHIP fee E117 "limited" keratectomy *	$308.30
	Epithelial abrasion - substitute OHIP fee Z871 - epithelial debridement *	$26.60
	Pachymetry - substitute OHIP fee G813 - corneal pachymetry *	$12.75
	Total cost (1 eye)	$662.23
	Total cost (2 eyes)	$1,324.47
Postoperative		
Ophthalmologist repeat visit	OHIP fee A234 - Partial assessment (First day)	$25.10
	OHIP fee A234 - Partial assessment (First week)	$25.10
	OHIP fee A234 - Partial assessment (First month)	$25.10
Corneal topography	First month measurement	$50.00
Medication	Antibiotic - moxifloxacin (Vigamox) *	$30.00
	Anti-inflammation (corticosteroid) - dexamethasone (Maxidex) *	$22.19
	Total cost (1 eye)	$177.49
	Total cost (2 eyes)	$229.68
Total aggregated costs		

Total cost per patient (1 eye)	$1,036.12
Total cost per patient (2 eyes)	$1,750.55

Note: The costs of items marked with an asterisk were doubled to estimate the cost of providing CXL therapy to both eyes.

Table 27: Total Annual Costs of CXL for Keratoconus – Estimated Physician, Clinic and Medication Costs*

Description	Existing cases (Prevalence)	New cases (Incidence)	Average annual
Number of patients			
Number of CXL keratoconus cases	4,047	148	1,497
Total cost - 1 eye per patient			
Physician costs	$2.71M	$0.10M	$1.00M
Clinic costs	$1.10M	$0.04M	$0.41M
Medication costs	$0.39M	$0.01M	$0.14M
Total cost	$4.19M	$0.15M	$1.55M
Total cost - 2 eyes per patient			
Physician costs	$4.12M	$0.15M	$1.52M
Clinic costs	$2.20M	$0.08M	$0.81M
Medication costs	$0.77M	$0.03M	$0.29M
Total cost	$7.08M	$0.26M	$2.62M
Average total cost			
Physician costs	$3.41M	$0.13M	$1.26M
Clinic costs	$1.65M	$0.06M	$0.61M
Medication costs	$0.58M	$0.02M	$0.21M
Total cost	$5.64M	$0.21M	$2.09M

*M indicates million

Appendices

Appendix 1A: Search Strategy

Clinical Search – Corneal Cross-Linking

Search date: April 28, 2011
Databases searched: OVID MEDLINE, MEDLINE In-Process and Other Non-Indexed Citations, OVID EMBASE, Wiley Cochrane, International Agency for Health Technology Assessment

Database: Ovid MEDLINE(R) <1948 to April Week 3 2011>, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <April 27, 2011>, EMBASE Classic+EMBASE<1947 to 2011 Week 16>
Search Strategy:

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1 expKeratoconus/ (6952)
2 (keratoconus or keratoectasia or keratectasia).ti,ab. (6636)
3 (cornea$ adj3 ectasia$).ti,ab. (555)
4 ((cone or conical) adj3 (ectasia or cornea)).ti,ab. (103)
5 or/1-4 (8555)
6 exp Cross-Linking Reagents/ (77205)
7 exp cross linking/ (100176)
8 exp Collagen/ (209586)
9 exp Riboflavin/ (23765)
10 exp PUVA/ (7733)
11 exp Ultraviolet Therapy/ (46824)
12 (riboflavin or PUVA or collagen).ti,ab. (278233)
13 (cxl or cross-link* or crosslink*).ti,ab. (126527)
14 or/6-13 (560410)
15 5 and 14 (774)
16 limit 15 to english language (637)
17 remove duplicates from 16 (374)

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Appendix 1B: Literature Search Strategies

Economic Search – Corneal Cross-Linking

Search date: May 3, 2011
Databases searched: OVID MEDLINE, MEDLINE In-Process and Other Non-Indexed Citations, OVID EMBASE, Wiley Cochrane, Centre for Reviews and Dissemination/International Agency for Health Technology Assessment

Database: Ovid MEDLINE(R) <1948 to April Week 3 2011>, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <May 02, 2011>, EMBASE Classic+EMBASE<1947 to 2011 Week 17>
Search Strategy:
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1 expKeratoconus/ (6955)
2 (keratoconus or keratoectasia or keratectasia).ti,ab. (6642)
3 (cornea$ adj3 ectasia$).ti,ab. (557)
4 ((cone or conical) adj3 (ectasia or cornea)).ti,ab. (103)
5 or/1-4 (8563)
6 exp Cross-Linking Reagents/ (77208)
7 exp cross linking/ (100207)
8 exp Riboflavin/ (23779)
9 exp Ultraviolet Therapy/ (46907)
10 exp PUVA/ (7747)
11 exp Collagen/ (209728)
12 (riboflavin or PUVA or collagen).ti,ab. (278420)
13 (cxl or cross-link* or crosslink*).ti,ab. (126631)
14 or/6-13 (560810)
15 5 and 14 (777)
16 limit 15 to english language (639)
17 remove duplicates from 16 (375)
18 exp Economics/ or exp Models, Economic/ or exp Resource Allocation/ or exp "Value of Life"/ or exp "Quality of Life"/ (1079508)
19 exp "Health Care Cost"/ or exp Health Economics/ or exp Resource Management/ or exp Economic Aspect/ or exp Economics/ or exp Quality Adjusted Life Year/ or exp Socioeconomics/ or exp Statistical Model/ or exp "Quality of Life"/ (1831216)
20 (econom* or cost* or budget* or price* or expenditure* or pharmacoeconomic* or pharmaco-economic* or valu* or discount* or afford*).ti,ab. (3572065)
21 (decision adj1 (tree* or analy* or model*)).ti,ab. (16871)
22 ((cost$ adj benefit$) or costbenefit$ or (cost adj effective$) or costeffective$ or econometric$ or life value or quality-adjusted life year$ or quality adjusted life year$ or quality-adjusted life expectanc$ or quality adjusted life expectanc$ or sensitivity analys$ or "value of life" or "willingness to pay").ti,ab. (162124)
23 or/18-22 (4934069)
24 17 and 23 (41)

Appendix 2: Additional Tables and Study Data

Table A1: Effectiveness Reports of Corneal Collagen Cross-Linking of Keratoconus*

Author, Year	Site Country	Study Design and Follow-Up	Population	Study Objective
Agrawal V, 2009 (49)	Clear Vision Eye Center, India	Retrospective pre-post longitudinal consecutive cohort Mean 10.1 ± 3.55 month (R, 6 to 16 months)	25 P – 37 e Progressive KC Mean age 16.9 yrs± 3.5 (R, 12 to 39 yrs)	To assess the impact of CXL at 1-yr follow-up in an Indian cohort affect with progressive KC
Arbelaez M, 2009 (50)	Muscat Eye Center, Oman	Prospective pre-post longitudinal cohort 1 year	19 P (14 M, 5 F) - 20 e Progressive moderate to severe bilateral KC Mean age 24.4 yrs (R,18 to 44 yrs)	To evaluate safety and effectiveness of CXL in improving visual acuity and stabilizing progression of KC
Caporossi A, 2006 (8)	Dpt Ophthalmology Siena University, Italy	Pre-post longitudinal cohort with untreated fellow-eye as control 6 months	10 P (8M, 2F) - 10 e Bilateral progressive low or moderate KC Mean age 31.4 yrs(R, 21 to 39 yrs)	To assess the effectiveness of CXL in reducing KC progression and improving vision
Caporossi A, 2010 (41)	Dpt Ophthalmology Siena University, Italy	Prospective pre-post longitudinal cohort with untreated fellow-eye as control 4 year	44 P – 44 e Progressive KC Age range 10 to 40 yrs	To assess the long term results of CXL for progressive KC
Doors M, 2009 (52)	Dpt Ophthalmology University Medical Center, Netherlands	Pre-post longitudinal consecutive cohort Mean 6.3 months ± 3.7 (R, 1 to 12-months	29 P - 29 e 28 progressive KC, 1 post-LASIK ectasia Mean age 35.1 yrs± 11.7 (R, 19 to 76 yrs)	To investigate the stromal demarcation line after CXL with optical coherence tomography and its impact on short term results in progressive KC

Author, Year	Site Country	Study Design and Follow-Up	Population	Study Objective
El-Raggal T, 2009 (53)	Dpt Ophthalmology, Ain Shams University Egypt	Pre-post longitudinal cohort 6 months	9 P (3 M, 6 F) – 15 e KC (Krumeich grade 1 – 111) Mean age 26.4 yrs (R, 21 to 31)	To evaluate the safety and effectiveness of CXL in reducing KC progression and evaluate the visual and refractive changes
Hersch P, 2011 (47)	Cornea and Laser Eye Institute – Hersch Vision Group and Dpt Ophthalmology New Jersey Medical School, New Jersey	Multicenter prospective RCT 1 year	58 P - 71 e (49 KC, 22 post-LASIkectasia) sham control 41 e (28KC, 13 post-LASIK ectasia) and control group 30 e (21 KC, 9 post-LASIK ectasia)	To evaluate the 1-year outcomes of CXL for treatment of progressive KC and LASIK<or photorefractive keratectomy induced corneal ectasia
Henriquez M, 2011 (44)	Oftalmo Salud Institute de Ojos, Peru	Pre-post longitudinal cohort and comparative untreated progressive KC control group 1 year	10 P (8 M, 2 F) – 10 e Progressive KC (Krumeich grade 1, 11) Mean age 29.7 yrs (R, 15 to 43)	To evaluate safety and efficacy of CXL for the treatment of progressive KC
Koller T, 2009 (55)	Institute for Refractive and Ophthalmic Surgery, Switzerland	Pre-post longitudinal cohort with untreated fellow-eye as control 1 year	21 P (15M, 6 F) - 21 e Mild to moderate KC (n = 8), pellucid marginal degeneration (n = 4) mixed (n = 9)	To compare by Scheimpflug imaging changes in corneal geometric shape after CXL in CXL treated and untreated cases progressive actasia
Leccisotti A, 2010 (46)	School of Biomedical Sciences, University of Ulster, United Kingdom	Pre-post longitudinal cohort with untreated fellow-eye as control 1 year	64 P Progressive KC Mean age 26.9 ± 6.3 yrs (R,18 to 39)	To evaluate clinical effects of trans-epithelial CXL in progressive KC
Raiskup-Wolf F, 2008 (6)	Department Ophthalmology, CG Carus University Hospital, Germany	Prospective pre-post longitudinal cohort Mean 26.7 months± 16.2 (R, 12-months to 6 years)	130 P – 241 e Progressive KC Mean age 30.04 yrs ± 10.46	To evaluate the long term effects of CXL in progressive KC

Author, Year	Site Country	Study Design and Follow-Up	Population	Study Objective
Saffarian L, 2010 (54)	Navid Didegan Eye Center, Iran	Prospective pre-post longitudinal cohort 1 year	53 P (31 M, 22 F)) – 92 e Progressive KC Mean age 21.5 yrs± 3.4 (R,16 to 30)	To evaluate outcomes of CXL for progressive KC in Iranian patients at 1 year
Vinciguerra P, 2009 (58)	Department Ophthalmology, Instituto Clinico Humanitas, Italy	Prospective pre-post longitudinal cohort with untreated as control 1 year	28 P (20 M, 8 F) - 28 e Progressive KC (grade 111 AK stage) with fellow untreated eye (1-11 stage) as control Range 24 to 52 years	To evaluate 1 year refractive, topographic, tomographic, and aberrometric outcomes after CXL for progressive KC
Vinciguerra P, 2010 (43)	Department Ophthalmology, Instituto Clinico Humanitas, Milano, Italy	Prospective pre-post longitudinal cohort with untreated as control 2 year	28 P (20 M, 8 F) - 28 e Progressive KC (grade 111 AK stage) with fellow untreated eye (1-11 stage) as control Range 24 to 52 years	To evaluate intra-operative and 2 year refractive, topographic, tomographic, and aberrometric outcomes after CXL for progressive KC
Wollensak G, 2003 (7)	Department Ophthalmology, Technical University of Dresden, Germany	Prospective pre-post longitudinal cohort with untreated fellow-eye as control Mean 23.2 months ±12.9 (R, 3 to 47 months)	22 P (12M, 10F) -23 e Moderate to advanced progressive KC with fellow untreated eye as control Mean age 31.7 yrs± 11.9 (R,13 to 58)	To evaluate the safety and effectiveness of CXL on the progression of KC

*CXL indicates corneal cross-linking; E indicates eye; KC indicates keratoconus; M indicates male, F indicates female; P indicates people; SD indicates standard deviation; Yrs indicates years.

Table A2: Adjunct Interventions with Corneal Collagen Cross-Linking and Intrastromal Corneal Ring Segments*

Author, Year	Site, Country	Study Design	Population	Duration

Author, Year	Site, Country	Study Design	Population	Duration
Coskunseven E, 2009 (61)	Dunya Eye Hospital, Turkey	Prospective RCT – Group 1 CXL followed by ICRS implantation and Group 2 ICRS implantation followed by CXL – treatment interval was 7 months	43 P (25 M, 18 F) – 48 e KC AC Grade 1 - 111	6-month
Chan C, 2007 (66)	Private practice, California, United States	Comparative series with matched groups: Group 1 with ICRS implantation only versus Group 2 with trans-epithelial CXL performed after ICRS implantation on the same day	21 P – 25 e	Group 1 = 102 ± 39 days Group 2 = 97 ± 38 days
El-Raggal T, 2011 (63)	Ain Shams University, Cairo, Egypt	Prospective comparative series with patients undergoing CXL followed by ICRS placement 6 months later and subdivided into 3 groups based on the power settings of the femtosecond laser used in ICRS placement – Group 11,5 mJ power setting, Group 2 1.6 mJ power setting and Group 3 1.7 mJ power setting. The control group, Group 4, did not have CXL.	20 P – 20 e Progressive grade 11-111 KC Age range 23 to 32	6-month
El-Raggal T, 2011 (62)	Ain Shams University, Cairo, Egypt	Prospective randomized comparative series with patients undergoing ICRS implanted with femtosecond laser followed by CXL performed in one session (7 e) or performed 6 months apart (9 e)	10 P (4 M, 6 F) – 16e Progressive mild to moderate KC Mean age 27.9 ± 4.8 yrs (R, 22 to 36)	12-months
Ertan A, 2009 (64)	Department of Cataract and Refractive Surgery, Kudret Eye Hospital, Turkey	Pre-post comparative cohort – ICRS implantation followed at 6 months with trans-epithelial CXL	17 P (10 M, 5 F) – 25 e Bilateral KC Mean age 25.14yrs (R,16 to 39)	First postop visit (after INTACS) was 3.98 months second postop visit (after CXL) was 2.67 months
Kamburoglu G, 2008 (121)	Kudret Eye Hospital, Turkey	Case report, ICRS implantation followed by trans-epithelial CXL the following day for postoperative LASIK ectasia	27-year-old male Post-LASIK ectasia	8 months

Author, Year	Site, Country	Study Design	Population	Duration
Vicente L, 2010 (65)	Boxer Wachler Vision Institute, California, United States	Prospective cohort, Simultaneous trans-epithelial CXL following ICRS implantation	10 P – 14 e KC Mean age 35 ± 13 yrs (R, 13 to 58)	3 year

*AK indicates Amsler-Krumeich grade; CXL indicates corneal collagen cross-linking; E indicates eye; ICRS indicates intrastromal corneal ring segment; F indicates female; KC indicates keratoconus; LASIK indicates laser in-situ keratomileusis; M indicates male; P indicates people; PMD indicates pellucid marginal degeneration; PRK indicates photorefractive keratectomy.

Table A3: Adjunct Interventions with Corneal Collagen Cross-Linking and Photorefractive Keratectomy*

Author, Year	Site, Country	Study Design	Population	Duration
Kanellopoulos A, 2007 (67)	Laser Vision Institute, Greece	Case report, CXL followed at 12-months by a topographically-guided PRK with untreated fellow- eye as control	26-year-old male Bilateral progressive KC	230-months
Kymionis G, 2009 (68)	Institute Vision and Optics, University of Crete Medical school, Greece	Case report, YAG laser PRK followed by CXL on the same day followed 15 days later by the procedures in the second eye	34-year-old female, bilateral KC (pellucid marginal degeneration)	12-months
Kymionis G, 2010 (70)	Institute Vision and Optics, University of Crete Medical school, Greece	Case report. Simultaneous excimer laser photorefractive keratectomy followed by CXL	24-year-old male Progressive KC	6-month
Kymionis G, 2009 (69)	Institute Vision and Optics, University of Crete Medical school, Greece	Case series, simultaneous customized topography-guided surface Nd: YAG laser ablation followed by CXL	12 p – 14 e Progressive KC Mean age 28 yrs (R, 20 to 39)	10.69 months (R, 3 to 16)
Kymionis G, 2010 (71)	Institute Vision and Optics, University of Crete Medical School, Greece	Case series, Simultaneous photorefractive keratectomy (PRK) followed by CXL	23 p – 28 e KC Mean age 30 yrs± 9.35 (R, 20 to 44)	6-month
Kymionis G, 2010 (72)	Institute Vision and Optics, University of Crete Medical School, Greece	Case reports, Simultaneous conductive keratoplasty (CK) followed within 24 hours by CXL	2 p Bilateral KC 22-year-old male, 23-year-old male	6-month
Stojanovic A, 2010 (73)	Eye Dpt University Hospital of North Norway, Norway	Case series, Simultaneous topographically-guided excimer laser surface ablation followed by trans-epithelial CXL	12 p – 12 e 6 KC, 6 PMD Mean age 39.8 ± 11.9 yrs (R, 26 to 62)	12-months
Kanellopoulos A, 2011 (74)	Laser Vision Institute, Greece	Case series, Simultaneous topographically-guided partial PRK followed by CXL	22 p – 32 e Post Lasik ectasia Mean age 32 yrs (R, 23 to 66)	27-months

*CXL indicates corneal cross-linking; KC indicates keratoconus; PRK indicates photorefractive keratectomy; R indicates range; Yrs indicates years;

Table A4: Safety Studies of Corneal Collagen Cross-Linking*

Author, Year	Site, Country	Study Design and Follow-Up	Study Population	Study Objective
Bakke E, 2009 (122)	Dpt Ophthalmology, Universities Ulleval, Oslo and Northern Norway	Pre-post consecutive prospective cohort 1 week	30 P (27 M, 3F) - 30 e Mean age 31.2 yrs± 9.5 (R, 18 to 53)	To compare the severity of postoperative pain and rate of penetration of riboflavin between eyes treated with CXL and having epithelial removal either mechanically of by excimer laser
Goldich Y, 2009 (101)	Dpt Ophthalmology, Assaf Harofeh Medical Center, Tel-Aviv, Israel	Prospective pre-post cohort 6 months	10 P (7 M, 3 F) – 10 e Mean age 26.5 yrs± 5.7 (R,18 to 37)	To assess biomechanical corneal properties, corneal hysteresis (CH) and corneal resistance (CRF) and compensated intraocular pressure (IOP)
Greenstein S, 2010 (94)	Cornea and Laser Eye Institute – Hersch Vision Group, CLEI Center for Keratoconus, New Jersey, United States	Prospective RCT – group 1: CXL treated (and fellow untreated eye as control) Group 2: sham riboflavin only 1 year	44 P (KC 31, post-LASIK ectasia 19) – 50 e and control group 41 e (28 KC, 13 post-LASIK ectasia)	To determine the natural history of CXL associated corneal haze with Scheimpflug 3-D corneal density and slit lamp biomicroscopic analysis
Greenstein S, 2011 (100)	United States	Multicenter prospective RCT 1 year	65 P [54 P (KC), 28 (post LASIK)] – 82 e with untreated fellow-eye as control and sham treated control group 41 e (28KC, 13 post-LASIK ectasia) and fellow untreated eye control 39 e (25 KC, 14 post-LASIK ectasia)	To evaluate the natural course of corneal thickness changes following CXL
Grewal D, 2009 (97)	Grewal Eye Institute Chandigarh, India	Pre-post longitudinal comparative cohort 1 year	102 P (55 M, 47 F) Progressive KC Mean age 25.6 yrs± 4.5 (R, 18 to 31 yrs)	To evaluate changes in corneal parameters using Scheimpflug imaging post CXL and to examine the effect of UVA exposure on lens density using rotating Scheimpflug imaging and foveal thickness using optical coherence tomography

Author, Year	Site, Country	Study Design and Follow-Up	Study Population	Study Objective
Knappe S, 2011 (104)	Dpt Ophthalmology, University of Rostock, Germany	Prospective pre-post longitudinal cohort	8 P (6 M, 2 F) - 8 e Progressive KC Mean age 33.6 yrs± 13.9	To evaluate the time course of corneal structural changes following CXL using confocal in vivo microscopy
Koller T, 2009 (55)	Institute for Refractive and Ophthalmo Surgery, Zurich, Switzerland	Pre-post comparative cohort 1 year	99 P (62 M, 37F) – 117 e Progressive mild to moderate keratectasia (KC, PMD)	To evaluate failure and complication rates in first postoperative year of CXL
Kymionis G, 2009 (90)	Institute of Vision and Optics, University of Crete, Greece	Prospective pre-post comparative cohort 1 year	10 P - 10 e Progressive KC (n = 5), post-Lasik ectasia (n = 5) Normal (n = 3), Normal post-LASIK (n = 3)	Compared structural changes using corneal confocal microscopy in post-LASIK ectasia and KC following CXL
Kymionis G, 2009 (99)	Institute of Vision and Optics, University of Crete, Greece	Prospective pre-post cohort 1 month	15 P (10 M, 5 F) – 19 e Mean age 26.9 yrs± 6,5 (R, 17 to 40)	To evaluate peri-operative pachymetric changes following CXL
Kymionis G, 2010 (102)	Institute of Vision and Optics, University of Crete, Greece	Prospective pre-post longitudinal cohort 1 year	55 P (55 e) Mean age 24.4 yrs±4.1 (R, 18 to 36)	To examine the effect of CXL on intraocular pressure (IOP) by Goldman applanation tonometry (GAT)
Lim L, 2011 (95)	Corneal Eye Dpt, Singapore National Eye Center, Singapore	Prospective pre-post cohort 3 month	30 P (2 case reports both age 23) Progressive KC	To examine safety and efficacy following CXL and review complications of deep stromal scarring post CXL in mild KC

Author, Year	Site, Country	Study Design and Follow-Up	Study Population	Study Objective
Mazzotta C, 2006 (105)	Dpt Ophthalmological Sciences, Siena University, Italy	Prospective pre-post cohort 6 month	10 P Progressive KC	To assess corneal tissue modifications and regeneration of epithelium and sub-epithelial nerve plexus by HRT 11 confocal microscopy following CXL
Mazzotta C, 2007 (91)	Dpt Ophthalmology and Neurosurgery, University of Siena, Italy	Prospective pre-post longitudinal cohort study 6 month	10 P (8 M, 2F) – 10 e Progressive low to moderate KC	To assess the ultrastructural modifications after CXL with HRT confocal microscopy in patients with progressive KC
Mazzotta C, 2007 (96)	Dpt Ophthalmology and Neurosurgery, University of Siena, Italy	Pre-post comparison with untreated fellow-eye as comparison 6 month	39 P – 40 e Bilateral KC (35 KC in Krumeich stage 1-11, 5 KC in stage 111)	To review 2 cases of stromal haze during the second and third postop month resistant to topical steroids
Mazzotta C, 2008 (92)	Dpt Ophthalmology and Neurosurgery, University of Siena, Italy	Pre-post longitudinal cohort 3 years	39 P – 44 e	To assess early and late corneal micro-morphological modifications with HRT 11 confocal microscopy following CXL
Mencucci R, 2007 (123)	Dpt Oto-Neuro-Ophthalmological Surgical Sciences, Eye Clinic, Italy	Case series Intra-operative	6 P (3 M, 3 F) – 6 e Bilateral progressive KC	To assess possible corneal thermal damage during CXL using in vivo surface thermographic analysis
Renesto A, 2010 (124)	Vision Institute, Dpt Ophthalmology, Federal University of Sao Paulo, Brazil	Prospective RCT (CXL group vs. riboflavin only) 3 months	32 P (9 M, 23 F) – 42 e CXL group (19 e): Mean age 29 yrs R, 17 to 55) , Control group (22 e): Mean age 31 yrs (R, 22 to 55)	Cytological examination of ocular surface changes following CXL
Sedaghat M, 2010 (103)	Eye Research Center, Mashhad University of Medical Sciences, Iran	Pre-post comparative study 6 months	51 P (31 M, 20 F) – 56 e	To compare the impact of CXL on 2 corneal biomechanical parameters, corneal hysteresis (CH) and corneal resistance factor (CRF) by waveform analysis

Author, Year	Site, Country	Study Design and Follow-Up	Study Population	Study Objective
Seiler T, 2006 (125)	Institute for Refractive and Ophthalmic Surgery, Zurich, Switzerland	Pre-post comparative cohort 2 weeks	16 P Progressive KC Mean age 26.4 yrs (R,18 to 39)	To investigate the CXL induced corneal stromal demarcation line between treated and untreated corneal stroma

*E indicates eyes; CXL indicates corneal cross-linking; F indicates female; KC indicates keratoconus; LASIK indicates laser in-situ keratomileusis; M indicates male; Mo indicates month; P indicates patients; PMD indicates pellucid marginal degeneration; Yrs indicates year.

Table A5: Complication Case Reports for Corneal Collagen Cross-Linking*

Author, Year	Indication	Complication Event	Outcome
Angunawela R, 2009 (83)	Case Report, 40-year-old patient with progressive KC treated with CXL.	Non-infective keratitis, treated with preservative-free levofloxacin and dexamethasone 0.1% followed by prednisone acetate 1% and topical agents	Complete resolution of infiltrates but with residual marginal corneal thinning
Gokhale N, 2010 (84)	Case report,19-year-old male with progressive bilateral KC treated bilaterally with CXL	1 week postoperatively presented with redness, watering, pain, loss of vision in his right eye. On exam right eye diffuse conjunctivitis, central corneal melt with severe thinning and perforation with adjacent edema.	A temporary cyano-acrylate glue applied bandage contact lens was applied until a donor cornea was available. A therapeutic keratoplasty was performed 5 days later. Histologic examination of the corneal button revealed central area of stromal loss with perforation. Stains for fungus and bacteria were negative.
Hafezi F, 2008 (87)	Case report, 33-year-old female. Post LASIK developed iatrogenic bilateral keratectasia during first pregnancy treated with CXL and resulting in exacerbation of keratectasia during second pregnancy	Bilateral iatrogenic keratectasia exacerbated during pregnancy	Not reported
Koppen C, 2009 (89)	Case report, 28-year-old female with bilateral progressive KC underwent CXL in right eye	On second postop day presented with redness, increasing pain and milky vision. On exam strong ciliary flush and presence of white superficial infiltrates. Cultures were negative and presumptive diagnosis of sterile keratitis that responded to high dose of topical corticosteroids.	At 1 year there was central and superior scarring in superficial stroma leading to a decreased visual acuity.
Koppen C, 2009 (89)	Case report, 17-year-old male with bilateral rapidly progressing KC underwent CXL in the left eye	On the second postop day presented with strong ciliary flush, white superficial infiltrates, and iritis with keratic precipitates. Cultures were negative. The epithelium defect healed slowly over 2 weeks. Iritis and keratitis responded to topical steroids.	At 7 months scar formation in the central stroma of the central cornea persisted leading to a decreased visual acuity resulting in subsequent keratoplasty .

Author, Year	Indication	Complication Event	Outcome
Koppen C, 2009 (89)	Case report, 23-year-old male with KC and intolerant to RGP lenses underwent CXL in right eye	On fourth postop day, strong ciliary flush, white superficial infiltrates over the treated zone. Responded to treatment involving sub-conjunctival injection of steroids and changed antibiotics to ofloxacin.	At 6 months visual acuity returned to baseline. The other eye did not undergo CXL.
Koppen C, 2009 (89)	Case report, 31-year-old male with bilateral KC underwent successful CXL in the right eye 3 months previous to the CXL in the left eye	At the first postop day, signs of pronounced inflammation, corneal edema, irregular epithelium and corneal infiltrates. Treated with sub-conjunctival injection of steroids.	At 5 months post op, visual acuity was reduced over baseline
Kymionis G, 2007 (78)	Case report, 21-year-old female with bilateral KC treated by CXL in right eye and planned penetrating keratoplasty in left eye	Herpetic keratitis with iritis On day 5 geographic epithelial defect, stromal edema and cells in the anterior chamber treated initially with topical steroids then to acyclovir with diagnosis herpes simplex virus	Decrease in stromal edema, presence anterior chamber cells and at 2 months a mild central corneal opacity remained
Kymionis G, 2007 (88)	Case report, 27-year-old male, CXL 4 years post LASIK for iatrogenic ectasia	Diffuse lamellar keratitis On first postoperative day inflammation with infiltrates covering the interface including the central cornea	After an intensive course every 2 hours of corticosteroid (dexamethasone 1%) inflammation responded rapidly and by 9th day infiltrates had resolved
Labiris G, 2011 (85)	Case report, 23-year-old male with bilateral progressive KC underwent CXL in the left eye	During the first postoperative day developed intense photophobia, watering and a nonspecific ocular discomfort. Intensive examination for autoimmune and infectious diseases were all within normal limits. Repeated cultures from the cornea and contact lens were negative.	Cornea presented slow re-epithelialization and progressive thinning resulting in descemetocele and perforation in the second month and underwent successful penetrating keratoplasty. Concluded that nonspecific irreversible damage to keratocytes resulting in corneal melting had occurred.
Mangioris G, 2010 (86)	Case report. 25-year-old female with bilateral KC underwent CXL.	Presented 5 days post CXL with multiple deep infiltrates in periphery of cornea near limbus. Corneal scraping and secretions were negative for organisms	At 2 months some nebulae remained in the central cornea and visual acuity was reduced.

Author, Year	Indication	Complication Event	Outcome
Perez-Santonja J, 2009 (79)	Case report, 29-year-old female with progressive bilateral KC. CXL in right eye for stage 1 KC and 1 month later ICRS implants in the left eye for stage 11 KC.	Microbial keratitis, photophobia and blurring in the CXL treated right eye, culture proven Staphylococcus epidermidis treated with topical ofloxacin 0.3% and tobramycin at 1-hr intervals.	Ocular inflammation and corneal infiltrates improved rapidly and at 5 months postop a mild haze was detected
Pollhammer M, 2009 (80)	Case report, 42-year-old patient with KC treated with CXL and postoperatively experiencing pain and progressive reduction in visual acuity	Stromal infiltrates and anterior chamber inflammation due to bacterial infection with Escherichia coli	Infection successfully treated after several weeks with tobramycin and cephazolin eye drops Resulted in avascularized corneal scar and permanent reduction of visual acuity
Rama P, 2009 (81)	Case report, 32-year-old man with bilateral KC treated with CXL in the left eye reported conjunctival redness and discharge 3 days postoperatively	Progressive corneal involvement with corneal opacification and despite intensive oral and topical antibiotics and steroids for infection with Acanthamoeba, persisting severe inflammation with corneal ectasia and subtotal de-epithelialization	Corneal ulceration with melting and cornea perforation on day 11 followed by penetrating keratoplasty. At 2 months the graft was clear with no sign of infection
Rodriguez-Ausin P, 2011 (76)	Case reports, 21-year-old patient with bilateral progressive grade 111 KC treated with CXL in the left eye and 9 months later CXL in the right eye. Referred for slight pain and low visual acuity in right eye 48 hours postoperatively	Corneal infiltrates with ulcer and despite 3 weeks intensive oral and topical antibiotic treatment (cultures were negative or bacteria or fungi) stromal opacities persisted at 3 weeks and at 2 months corneal leucomas and inferior thinning	At one year, KC stabilization was reported and a bilateral toric ICL implantation significantly improved bilateral visual acuity
Rodriguez-Ausin P, 2011 (76)	Case report, 11-year-old male with grade 3 to 4 KC treated initially with contact lenses to improve visual acuity and subsequently treated with CXL for bilateral progressive KC	After CXL 48 hours sterile corneal infiltrates (cultures negative for bacteria, fungi or parasites) and after intensive antibiotic and steroid treatment at 3 months detected in right eye stromal haze and stromal inflammatory infiltrates	At 12-month F-up the right eye showed progression, worsening of best corrected visual acuity with contact lens (1 line lost) and grade 2 para-central scarring
Sharma N, 2010 (82)	Case report, 19-year-old female with KC underwent CXL in the right eye and on fourth postop day presented with 3-day history of pain, redness and decreasing vision in the right eye	On exam corneal infection along with a corneal ulcer with central infiltrates with epithelial defect involving 90% of the corneal depth. Corneal scrapings were positive for Pseudomonas aeruginosa which responded to antibiotic treatment	At 2 months infiltrates decreased in size and a leucomatous corneal opacity remained with greatly reduced visual acuity. An optical keratoplasty is planned for visual rehabilitation.

Author, Year	Indication	Complication Event	Outcome
Zamora K, 2009 (77)	Case report, 32-year-old male with KC underwent CXL in the left eye and presented on the third postop day with a 1-day history of red painful eye.	On exam conjunctival infection, severe keratitis with central corneal epithelial defect, ring of infiltrates and dense fibrin reaction throughout the anterior chamber. Cultures from the contact lens were positive for Streptococcus salivarius and S oralis. And corneal scrapings were positive for Staphylococcus sp.	At 2 months, residual central corneal stromal haze and a sub-epithelial scar in a ring-like configuration remained

*CXL indicates corneal cross-linking; ICRS indicates intrastromal corneal ring segment; KC indicates keratoconus; RGP indicates rigid gas permeable.

Table A6: Impact of CXL on Corneal Curvature in Keratoconus – Pre-Post Longitudinal Higher Order Topographic Outcomes*

Author, Year	Patients (P) Mean Age± SD	Keratometric Outcome	*Baseline* Diopters Mean ± SD	Diopters Mean ± SD	*Difference* Diopters Mean ± SD	*P-Value*
Agrawal V, 2009 (49)	25 P (37 e) 16.9 ±3.5 years	K-Max, K-Apex 12-Month (Keratron Scout, Optikon, Italy)	53.26 ± 5.93 D		-2.47 ± 3.89 D -2.73 ± 7.95 D K-Max summary Decreased (± 1.0D) 54% (20/37) Stable (± 0.5D) in 38%(14/37) Worse (>-1.0 D) 8% (3/37)	0.004 0.004
		Corneal wavefront surface aberrometry			Spherical and higher order corneal aberrations did not show significant changes Coma component (lower order aberrations) showed significant reduction	Coma 0 .003
Arbelaez M, 2009 (50)	19 P (20 e) 24.4 (R,18 to 44) years	K- Average K- Apex at 12-months	49.93 ± 5.02 D 51.89 ± 7.99 D	48.57 ± 4.54 D 50.42 ± 8.09 D	1.36 D 1.40 D	0.004 0 .01

Author, Year	Patients (P) Mean Age± SD	Keratometric Outcome	*Baseline* Diopters Mean ± SD	Diopters Mean ± SD	*Difference* Diopters Mean ± SD	*P-Value*
		Corneal wavefront surface aberrometry			Spherical and higher order corneal aberrations did not show significant changes Absolute RMS and absolute coma were significantly reduced	0.041 0.026
Doors M, 2009 (52)	29 P (29 e) 35.1 ±11.7 years (R, 19 to 76)	Central K K-Max at 6 months Corneal topography (Eye map), Pentacam HR tomography (Oculus),			Mean central K and K-Max were not significantly changed	> 0 .05
		Corneal aberrometry (IRX-3 Wavefront Aberrometer)	Coma-x -0.05 ± 0.38 µm Coma-y -0.19 ± 0.92 µm Spherical aberration 0.12 ± 0.27 µm	-0.19 ± 0.39 µm -1.10 ± 0.91 µm 0.07 ± 0.30 µm	Higher-order aberration values coma-x, coma-y and spherical aberration were not significantly changed	> 0 .05

Author, Year	Patients (P) Mean Age± SD	Keratometric Outcome	*Baseline* Diopters Mean ± SD	Diopters Mean ± SD	*Difference* Diopters Mean ± SD	*P-Value*
El-Raggal T, 2009 (53)	9 P (15 e) 26.4 (R, 21 to 31) years	K-average	47.77 ± 1.79 D (R, 44.8 to 50.1)	46.27 ± 1.66 D (R, 43.6 to 48.7)		< 0.001
		K-Max At 6 months	52.17 ± 1.66 D (R, 49.2 to 54.1)	50.42 ± 1.57 D (R, 47.9 to 52.7)		< 0 .001
		Corneal topography (TMS-4 Tomey Inc)				
Raiskup-Wolf F, 2008 (6)	130 P (142 e) 30 ± 10.5 years	K-Apex			-2.68± 7.61 D	< 0 .01
		K-Max At 12-months			-1.46 ± 3.76 D	< 0.01
					K-Apex decreased in 62% eyes, remained stable in 17% and increased in 21%	
Saffarian L, 2010 (54)	53 P (92 e) 21.5 ±3.4 (R,16 to 30) years	Sim-K Corneal topography by Orbscan 11 -	46.94 ± 2.37 D	46.0 ± 2.33 D	0.94 ± 0.71 D	< 0.001

*E indicates eye, K indicates keratometry; Max indicates maximum; P indicates people.

Table A7: Impact of CXL on Corneal Curvature in Keratoconus – Higher Order Topographic Findings in Treated and Untreated Fellow-Eyes*

Author Year	Patients (P) Mean Age	Keratometric (K-Value) Outcome	Treated Eye Diopters Mean ± SD	Untreated Eye Diopters Mean ± SD	Pre-post change Treated Vs Untreated Eye
Caporossi A, 2010 (41)	44 P (44 e) Range 10 to 40 years	K- Average at 12-months Corneal topography (CSO Eye Top,	Pre-post change -1.96 ± 0.63 D (R, 0.92 to -3.24)	Pre-post change +1.2 ± 0.96	
		Surface aberrometry (CSO Eye Top)	Pre-post change Total wavefront higher order aberrations significantly reduced (*P* <0 .00001)		
		Corneal symmetry- Inferior-Superior-inferior index (SI)	Pre-post SI asymmetry index significantly improved (*P* < 0.0001) Spherical aberration remained unchanged		
Henriquez M, 2011 (44)	10 P (10 e) and 10 control P (10 e) 29.7 (R, 15 to 43) years	K-Max K-Min At 12-months Corneal typography Topcon	Pre-post reduction K-Max 2.66 D p = .04 K-Min 1.61 D (*P* = 0.03) 80% (8/10) decreased K-Max 20% (2/10) worsening K-Max	90% (9/10) had increased K-Max	
Koller T, 2009 (45)	21 P (21 e) Age NR	Corneal topography Pentacam system with Scheimpflug camera – progression regression minimum corneal curvature radius (Rmin/mm) At 12-months	Pre-post improvement Rmim/mm 6.14 to 6.21 (*P* = 0.01)	Pre-post worsening Rmin/mm 6.94 to 6.86 (*P* = 0.002)	Pre-post change Rmin/mm 0.066 ± 0.10 vs -0.08 ± 0.10 (*P* = 0.0009) Rmin/D

Author Year	Patients (P) Mean Age	Keratometric (K-Value) Outcome	Treated Eye Diopters Mean ± SD	Untreated Eye Diopters Mean ± SD	Pre-post change Treated Vs Untreated Eye
			Rmin/D 55.0 D to 54.3D (*P* = 0.01) 4 / 7 Pentacam KC indices showed significant improvements towards a more normalized corneal anterior surface	Rmin/D 48.6 to 49.2 (*P* = 0.002) Based on ΔRmin 0.12 mm ≈ 1 Progressed = 7 untreated Vs 0 treated Unchanged = 14 untreated Vs13 treated Regressed = 0 untreated Vs 8 treated	-0.62 ± 0.9 vs 0.57 ± 0.8 (*P* = 0.0009)
Leccisotti A, 2010 (46)	51 P (51 e) 26.9 ± 6.3 (R 26.9 to 39) years	K-Apex Average Sim-K (averaging flattest and steepest meridian) At 12-months	Pre-post K-Apex 54.31 ± 8.76 to 54.81 ± 4.86 Mean Δ 0.51 ± 7.79 (*P* >0.05) Pre-post Sim-K 46.63 ± 2.89 to 46.53 ± 3.18 Mean Δ -0.10 ± 1.44 (*P* > 0.05)	Pre-post K-Apex 51.69 ± 6.42 to 53.30 ± 7.71 Mean Δ 1.61 ± 6.28 (*P* > 0.05) Pre-post Sim-K 44.60 ± 2.19 to 45.48 ± 2.88 Mean Δ 0.88 ± 2.35 (*P* > 0.05)	Comparative Pre-post Δ K-Apex (95% CI) -3.98 to 1.87 Comparative Pre-post Δ Sim-K (95% CI) -1.75 to -0.21
		Corneal surface regularity	Pre-post	Pre-post	Comparative Pre-post Δ

Author Year	Patients (P) Mean Age	Keratometric (K-Value) Outcome	Treated Eye Diopters Mean ± SD	Untreated Eye Diopters Mean ± SD	Pre-post change Treated Vs Untreated Eye
		index (ISV) -deviation of individual corneal radii from mean values (abnormal >37) At 12-months Tangential video keratography (Keratograph	ISV 76.4 ± 28.2 to 77.3 ± 28.8 Mean Δ 0.9 ± 4.69 (*P* > 0.05)	ISV 48.2 ± 14.3 to 53.5 ± 19.5 Mean Δ 5.3 ± 7.30 (*P* > 0.05)	ISV (95% CI) 1.99 to 6.81
Vinciguerra P, 2009 (48)	28 P (28 e) Range 24 to 52 years	K-Min K-Max Sim-K Corneal topography with CSO Eye Top Topographer and 21-Klyce indices	Pre-post K-Min 46.10 to 40.22 (*P* = 0.0003) K-Max 50.37 to 44.21 (*P* = 0.0011) Sim-K 48.08 to 42.01 (*P* = 0.0004)		
		Total (corneal and internal) wavefront analysis performed with Nidek OPD-Scan – 21-Klyce Indices	Pre-Post Sim-K1 50.53 to 50.13 (*P* < 0.05) Sim-K2 45.89 to 45.76 (P < 0.05) K-Min 41.18 to 41.32	Pre-Post Sim-K1 45.81 to 46.21 (*P* < 0.05) Sim-K2 43.29 to 43.57 (P < 0.05) K-Min 40.83 to 40.92	

Author Year	Patients (P) Mean Age	Keratometric (K-Value) Outcome	Treated Eye Diopters Mean ± SD	Untreated Eye Diopters Mean ± SD	Pre-post change Treated Vs Untreated Eye
			(*P* > 0 .05)	(*P* > 0.05)	
Wollensak G, 2003 (7)	22 P (23 e) 31.7 ±11.9 (R 13 to 58) years	K-max At 12-months Videokeratoscope (C-scan)	Pre-post K-Max Mean regression of 2.01 ± 1.74 D (p = .03) K-Max Regression in 70% (16/23) with average reduction 2.01 D (95% CI; 1.23 to 3.07) Stable in 22% (5/23) Increase in 1 patient of 0.28 D	K-Max progression on average 1.48 D in 22% (5/22)	
Hersh P, 2011 (47)	58 p (71 e) 41 KC and e	K-Max K-Average K-Min (Flat) K-Max (Steep) At 12-months Topography Scheimpflug camera (Pentacam)	Pre-post Treated Eye K-Max 60.4 ± 9.99 to 58.4 ± 8.41 (p < .05) K-Max Mean Δ 1.5 D (p< .001) K-Average 50.4 ± 7.06 to 48.9 ± 5.48 (p< .05) K-Steep 52.9 ± 7.45 to 51.5 ± 5.94 (p< .05) Δ K-Max Decrease ≥ 2 D(N=22), 1-2 D (N = 14), No change (N=28), Increase 1-2 D (N = 4), Increase ≥ 2 D	Pre-post Sham Group K-Max, K-Average, K-Steep – No statistically significant changes Pre-post Fellow-eye Δ K-Max +0.29 ± 1.19 D (p = .19) Δ K-average +0.20 ± 0.79 (p = .18)	Comparative pre-post Δ Treatment Vs Sham Group Only 3 month comparison as all crossed over No significant differences in kerotometry Comparative pre-post Δ Treatment Vs Untreated Fellow-eye Δ K-Max p < .001 Δ K-Average p < .001

*CI indicates confidence interval; E indicates eye, K indicates keratometry; Max indicates maximum; Min indicates minimum; NR indicates not reported; P indicates people; Sim indicates simulated; SD indicates standard deviation.

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